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Biotech CIP Cycle Development: Case Study Examples Utilizing QRM

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This article presents case study examples of CIP cycle development activities and lessons learned from several modern biotechnology facilities. The CIP Cycle Development program incorporates aspects of Quality Risk Management (QRM) to meet the needs of the biotechnology industry in today's regulatory environment.

A Clean-In-Place (CIP) Cycle Development (CD) program for a large scale biotech manufacturing facility was described in the September/October 2004 issue of *Pharmaceutical Engineering*. A three stage program of water, chemical, and soiled CIP CD and a project execution strategy utilizing the *ISPE Baseline® Commissioning and Qualification Guide* were presented. The purpose of the CIP CD program was to identify and resolve cleaning challenges prior to beginning the Cleaning Validation (CV) program. This follow up article will present practical case study examples and describe the manufacturing efficiencies gained. Finally, some aspects of Quality Risk Management (QRM) will be addressed as they apply to CIP CD. This article is not intended to be a complete overview of QRM concepts.

QRM Applied to CIP CD

QRM applied to the pharmaceutical industry is intended to protect the patient from adulterated drug products. The ICH Harmonized Tripartite Guideline Q9, Annex II, explains the potential applications for QRM. Annex II.3 (QRM as Part of Development) and Annex II.4 (QRM for Facilities, Equipment, and Utilities) can be interpreted in part to promote the use of CIP CD as a risk management tool based on the examples cited. Annex II.3 lists one purpose of QRM to be:

> *"To establish appropriate specifications, identify critical process parameters, and establish manufacturing controls."*[1]

Annex II.4 provides another example:

> *"To determine acceptable cleaning validation limits."*[2]

The cleaning of equipment through the use of validated procedures may mitigate the risk of producing adulterated drug products. Therefore, QRM principles can be applied to CIP CD and CV to identify important risk factors to be eliminated or minimized to acceptable levels.

How then might QRM be used to develop a CIP CD program and validated cleaning cycles? Annex I (Risk Management Tools and Methods) describes several structured approaches to QRM. Formal methodologies can be applied, including Failure Mode Effects Analysis (FMEA), Failure Mode Effects and Criticality Analysis (FMEAC), and Hazard Analysis and Critical Control Points Analysis (HACCP). Case study examples of these structured risk assessment approaches to CV and equipment cleaning and hold strategies have been published.[3]

However, Q9 also states the following:

> *"The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable."*[4]

A structured approach to CIP CD focusing on the development of cleaning control parameters, yields data which can be used to mitigate risk of product contamination. Defined as such, CIP CD is an informal risk management tool. The data gathered during a CIP CD program can be used to determine control and alarm setpoints and ensure cleaning cycles are robust, repeatable, and efficient. Practically speaking, operational knowledge gained by the end users results in improved cleaning procedures and enhanced personnel training.

Finally, the *FDA's Guide to the Inspection of Cleaning Validation Processes* states the following:

> *"It is not unusual to see manufacturers use extensive sampling and testing programs following the cleaning process without ever really evaluating the effectiveness of the steps used to clean the equipment."*[5]

This guidance document does not explicitly recommend a structured approach to CIP CD. However, a CIP CD program does facilitate the methodical evaluation of steps used to clean the equipment when the program includes all the manufacturing and quality stakeholders.

Practical Examples of CIP CD Issues

Having established that CIP CD is an informal risk management tool and can be used for cleaning process data analysis, two questions remain:

1. What are some practical lessons learned from a CIP CD program?
2. What efficiencies can be gained which demonstrate a Return On Investment (ROI), in a CIP CD program?

The first question will be addressed in a general manner that describes case study examples that could be applied to any biotechnology manufacturing facility that utilizes automated CIP cycles. The second question cannot be answered completely. How can one quantify the cost savings to a project of problems resolved during CIP CD that otherwise would have been encountered during validation lots or at some point in the life cycle of the facility? The best way might be to profile two similar projects, one which included a CIP CD program and another which did not, and to somehow quantify the project and product life cycle costs incurred by both resulting from cleaning problems. This type of analysis is beyond the scope of this article so "order of magnitude" estimate methods will be used. However, the benefit of manufacturing improvement projects has become so obvious to some big-pharma companies that they have stated a policy of:

> *"...treating projects to improve manufacturing as a research investment: anyone who proposes such a project does not have to submit a return-on-investment analysis."*[6]

QRM is a "new" development in the pharmaceutical industry. CIP CD is not new and there is no single correct method to plan and execute a CIP CD program. Each project must account for limitations imposed by cleanability studies, equipment availability, procedures, resources, objectives, time, and money. However, all well executed CIP CD programs have the following common characteristics:

1. a clear definition of system boundaries and mechanical configuration
2. detailed knowledge of the automation specifications
3. definition of an engineering/science rationale for the values of configurable parameters associated with the CIP cycle
4. understanding of equipment, CIP circuit, and residue grouping strategies
5. understanding of the critical cleaning process control parameters: time, temperature, flow, chemistry, and cleaning action
6. definition of a scope of work via a protocol, study, or checklist which defines the acceptance criteria that all stake holders pre-approve
7. good project management skills used to execute the work with available resources based on a schedule and budget
8. assurance that the goals of the CIP CD program align with the requirements of the Cleaning Validation program
9. definition of CIP CD and CV completion based on acceptable analytical results, repeatability, and cycle time. What constitutes "done?"

The CIP CD approach utilized a three step process of optimizing a CIP cycle: functional check-out with water, chemical CIP cycle testing (no soil) to confirm circuits can be rinsed of detergent residue, and finally, some degree of a soiled challenge. An assessment of risk tolerance determined the level of soiled CIP circuit sampling required prior to proceeding to cleaning validation.

The following points outline practical lessons learned applicable to any biotech process which utilizes automated CIP cycles and identifies potential risk mitigation areas.

Define Cleaning User Requirements

In general, User Requirement Specifications (URS) should be developed prior to beginning the design and construction of any biotech facility. If this has not occurred, the first step of the CIP CD program should be to assemble all the stakeholders (manufacturing, engineering, quality, and validation) and agree on cleaning user requirements for each CIP circuit type. The user requirements should specify "what" the CIP cycle process should accomplish to meet chemistry, temperature, time, flow, and cleaning action specifications. The CIP CD team will then utilize the equipment, automation, and configurable parameters to establish "how" the user requirements are implemented. It is important to understand the distinction between "what" and "how."

The vendor should be included in the user requirement development process for specialty equipment such as centrifuges, Tangential-Flow-Filtration (TFF) skids, and homogenizers. Examples of user requirements to define for TFF skids are: required shear rate, rinse/wash volumes, and temperature ranges, chemical concentrations, dirty and clean wet hold strategies, post CIP membrane storage requirements, and steam or chemical sanitization requirements. Centrifuge user requirement definition includes: product contact surface area boundaries, volumetric flowrate/throughput and backpressure specifications, discharge frequency and interval length, and valve composite cycle timing for parallel paths. ASME BPE 2001, Section SD-4.15 CIP Systems and Design also should be referenced when defining a URS for vessel and piping circuits. The URS should be preapproved by all stakeholders prior to starting the CIP CD program.

CIP CD Equipment Issues

Identify the Appropriate CIP Chemistry and Temperature

An assessment of the proper cleaning chemistry and tem-

perature is a critical aspect of the development of a CIP CD program. The FDA's guide states that:

> *"As with product residues, it is important and is expected that the manufacturer evaluate the efficiency of the cleaning process for the removal of residues. However, unlike product residues, it is expected that no, or for ultra sensitive analytical methods very low, detergent levels remain after cleaning. Detergents are not part of the manufacturing process and are only added to facilitate cleaning during the cleaning process. Thus they should be easily removable. Otherwise, a different detergent should be selected."*[7]

"Cleanability" studies utilizing soiled "coupon" testing may identify the proper cleaning chemistry and temperature at a bench top scale. The CIP chemical vendor also can be contracted to conduct a cleanability study. Studies should assess different materials of construction and unit operations. TFF membranes usually require cleaning chemistries and temperatures that are different than all other unit operations. Establishing specifications for each unit operation may minimize the need to test multiple CIP chemistries at the production scale. The "worst-case" soil may be identified and used to develop CIP circuit group testing strategies for CD and CV. There may be cases of residues that prove difficult to remove that cannot be predicted from coupon studies and must be tested at full scale.

Batch Chemical Solutions Effectively

After the wash concentration and temperature are defined, the CIP CD program will establish a repeatable method to batch solutions. The strategy employed will be a function of the CIP skid design. Is the chemical dosing controlled based on volume or time? Are chemicals delivered via a distribution header or drum pump? Volume based dosing systems will measure the quantity of wash water delivered into the wash tank and meter in the correct volume of chemical. Time based systems will open the chemical delivery valve based on a configurable parameter determined during CIP CD. Time based systems running off of a distribution header may deliver variable dose volumes due to fluctuations in pressure. In either case, testing at minimal, nominal, and maximum wash volumes is recommended. The required mixing time on the CIP skid should be determined for multiple wash volumes to ensure the required solution homogeneity is achieved.

Rinse Time Constraints

A typical CIP cycle utilizes single pass rinses and recirculated washes. The single pass rinse configuration can present challenges if the rinse water reservoir is limited in size compared to the CIP circuit hold-up volume. An engineering basis should be developed for establishing the minimum rinse time. Utilizing the volumetric flowrate, the circuit hold-up volume (which is often significant), and the rinse time, the CD team can estimate the rinse volume required. For large scale biotech facilities, it is not unusual to use single pass flow requirements on the order of 200-300 gallons at 50 gpm. Delivering this amount of water may require multiple rinse tank batching. Excessive rinsing can significantly increase water use, generate excessive waste, and add hundreds of hours of CIP cycle time during the course of a production campaign. Specifying a rinse time that is robust enough to remove chemical and process residues in a minimal amount of time can be accomplished in a number of ways, including specifying circuit turnover volumes, monitoring return conductivity, and obtaining grab samples. These can be analyzed for Total Organic Carbon (TOC), conductivity, pH, bioburden, and endotoxin levels.

Vessel Cleaning

The important points to consider in vessel cleaning include: ensuring adequate spray coverage as defined by ASME BPE 2001, Section SD-5.1 (Sprayball Test), minimizing pooling in the vessel, and ensuring turbulent flow through all inlet pathways. It is common practice to design vessel spray devices and conduct riboflavin coverage tests on vessels at 2.5-3gpm/linear foot of tank circumference. The CD team should ensure that the flowrate for vessel cleaning is the same used for sprayball coverage tests within allowable tolerances. The ASME recommends +/- 20% of rated flow. Verifying that the CIP skid can deliver the specified flow through a complex piping network will ensure proper coverage and drainage of rinse and wash solutions. The primary cleaning action in a vessel is fluid impingement and flow of a turbulent sheet on the sidewall. Pooling in the vessel bottom dish impedes this mechanism and can be minimized by using overlay pressure and/or a Clean In Place Return (CIPR) pump. Vortex breakers decrease air entrainment and will reduce pooling. Vessels CIP circuits often include complex valve cycling composite functionality designed to clean diptubes, entry ports, and inoculation lines. Ensuring turbulent flow through these parallel paths and adequate volume turnover should not be overlooked. Agitators and other internal parts should be installed in the vessel during the riboflavin coverage test and inspected to ensure proper coverage.

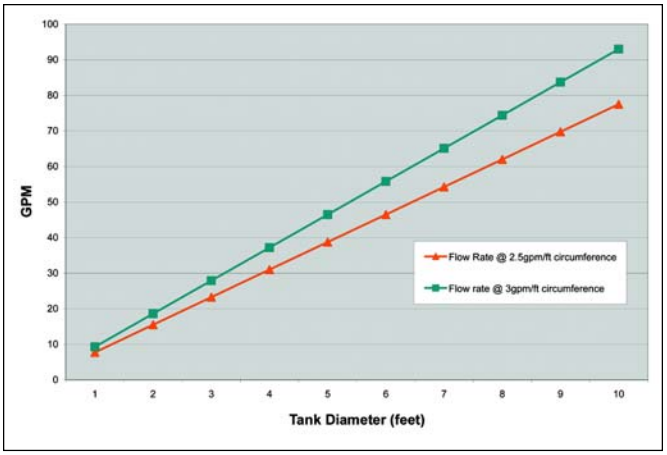

Figure 1. Sprayball coverage flow using ASME recommendations. Vertical cylindrical vessels with dished heads.

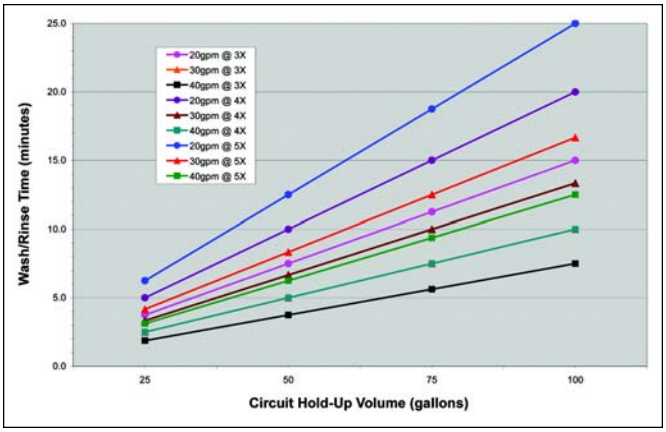

Figure 2. Wash/Rinse time for transfer line cleaning based on turnover volume. 3X, 4X, 5X for flowrates of 20gpm, 30gpm, and 40 gpm.

Identify Dead Legs with a Chemical CIP Cycle

A dead leg can be commonly described as a section of the CIP circuit which does not experience flow in the turbulent regime as defined by the Reynolds number. These areas can hold up residue or detergents and could result in product contamination and/or excessive rinse times. It is common in modern manufacturing facilities to achieve Length/Diameter (L/D) ratios of two or less.[8] Dead legs can be identified by running a chemical CIP cycle without soil. CIP final rinse failures may occur during this portion of testing due to dead legs, valve cycling issues, or inadequate pipe velocities. Automation and/or mechanical changes are required to fix these deficiencies. Chemical CIP cycle CD can be expedited by using CIP circuit grouping strategies based on mechanical similarities. The most conservative approach is testing with caustic and acid washes enabled irregardless of CV strategy. The equipment should not be soiled for the first time without data (via a CIP chemical test) demonstrating a high degree of assurance that residues can be removed. This is often overlooked during fast paced start-up schedules where firms are under pressure to start test batches as quickly as possible.

Transfer Line Cleaning

Transfer line cleaning CIP CD is more challenging than it may appear. A velocity of 5 ft/sec is frequently cited as necessary to ensure complete wetting and sweeping away of air pockets, particularly at high points in the system.[9] If the tubing is not wet, it will not be cleaned. Difficulties can be encountered when implementing volumetric flow rates at 5ft/sec. Rarely is a transfer line one pipe diameter size along its complete length beginning at the Clean In Place Supply (CIPS) header through the process line and returning through the CIPR header. For these circuits, establishing 5ft/sec flow in the largest diameter within the circuit is not always possible. In-line reducers, filter housings, and other fittings may impose pressure drop restrictions. A CIP CD specification that may be used to determine wash and/or rinse time length is the turnover ratio. Once the hold-up volume is known, a turnover ratio of three to five times for example, may be employed as a way to ensure lines receive an equivalent amount of cleaning. The hold-up volume can be determined by measuring the change in the wash tank level during recirculation. The simple formula below can be used to determine overall wash time: (Hold-up Volume X Turnover Ratio)/(Volumetric Flow) = Wash Time. The appropriate turnover ratio and hold-up volumes should be documented during CIP CD. This formula is a starting point only and its efficacy must be verified through sampling or in-line measurements.

Recirculated and Single Pass CIP Circuits

The mechanical configuration of CIP circuit boundaries may be designed as single pass circuits. For these circuits, wash and rinse solutions are not returned to the CIP skid, but are pumped through the CIP circuit directly to drain. Achieving required rinse times for one pass circuits is generally not a constraint since most rinses are directed to drain at the CIP skid anyway. Ensuring enough wash volume is available may be difficult however. For instance, a circuit with a hold-up volume of 250L might have the following restrictions utilizing the formula outlined above: (250L X 5)/100LPM = 12.5 minutes of wash time required. For this example, if the CIP skid wash tank volume is not at least 1250L, the functionality of the CIP skid will need to permit multiple tank washes, which adds a significant amount of cycle time.

Tangential Flow Filtration (TFF) Skid CIP CD Issues

The vendor should be consulted about the proper TFF CIP chemicals, temperature, shear (flow) requirements, and exposure times. The retentate side of the membrane is cleaned by "shear" while the permeate side cleaning is a function of Trans Membrane Pressure (TMP). Generally, cleaning and rinsing the permeate side of the membrane and the permeate piping is more difficult than cleaning the retentate side. This is because CIP solutions are forced through the membranes using TMP, but may not be at a rate which permits flow in the permeate piping of 5ft/sec. TFF systems may be mechanically configured to permit flow directly to waste from the permeate or retentate lines. During soiled testing and cleaning validation, rinse sample sites should be designated for these locations.

Centrifuge CIP CD Issues

The centrifuge is arguably the most mechanically complex "non-vessel" utilized in the biotechnology manufacturing operation and can be challenging to clean. The vendor should be involved early in a project to specify the cleaning URS so that proper CIP operation can be designed into the CIP cycle. For the disk stack type centrifuge, definition of product contact surfaces in the bowl should be accomplished during CIP CD with the aid of a detailed mechanical drawing of the bowl internals. Swabbing these areas requires disassembly. This activity should be carried out by trained individuals in a manner that does not compromise the sample site. The product contact surface areas in the bowl internals are subject to the same visual inspection requirements for visible residue and moisture that are applied to other equipment.

Bioreactor CIP CD Issues

The bioreactor is typically the most mechanically complex "vessel" utilized in a biotechnology facility. Developing the swab sample plan for a bioreactor will require the assessment of many swab sites based upon the mechanical design. Ensuring that coverage testing has been properly carried out is a pre-requisite for a successful CIP CD program. Ideally, the coverage test will document the minimum amount of time necessary to rinse the surface clear of riboflavin. This information can be used to develop an optimized wash time exposure for the tank internals where one might specify, for example, that the wash time be equivalent to three to five times the sprayball coverage time as a starting point. The cycle development study can focus on increasing or decreasing the time based on the analytical and visual results. This is critical for efficient CIP cycle times because of the number of "parallel paths" that are cleaned with the vessel. A detailed analysis of the hydraulic balance of the CIPS flow with the specified valve cycling composite will ensure fluid turbulence through piping and proper spray coverage. The sparge tube is often utilized as a pathway for CIP solutions to clean the bottom of impellers.

Portable Vessels, Depth Filter, and Hose Cleaning CIP CD Issues

Portable vessels, depth filters, and hoses present unique cleaning challenges. Portable vessels are usually the least mechanically complex biotech equipment; however, cleaning is not always straight-forward. Portable tanks in the range of 50 to 300 liters typically have low sprayball flow rates on the order of 10 to 20 gpm. If a single tank is cleaned at a utility panel and tied into a CIPR header and pump via a hose, the low flow rate to the vessel sprayball may limit the ability to rinse out the CIPS and CIPR lines efficiently because turbulent flow is not being supplied to the piping. Depth filters can present unique challenges due to the configuration of the housing flange/o-ring mechanical design. Special care needs to be made when specifying this interface to ensure that chemical or residue hold-up is not an issue in and around the o-ring. CIP skid cycles for hoses should be configured with the same velocity and turnover volume requirements used for hard piped transfer lines. Consideration should be given to the logistics of tracking dirty and clean hoses during CIP CD and incorporated in cleaning procedures.

CIP CD Instrumentation Issues

Diaphragm Failures and Valve Faults

An automated CIP cycle may fail and enter a HOLD state for a variety of reasons. Two sources of failures encountered during CIP CD are valve fault alarms and diaphragm valve failures. The valve faults encountered are typically related to a faulty limit switch or a valve that is not able to close because a line is full of liquid. A more difficult problem to solve from a CIP CD perspective is detecting a failed diaphragm. In this failure mode, the valve actuator and limit switch combination will stroke full open and closed without any fault. However, because the diaphragm has torn away from the actuator, the CIP flow path is blocked resulting in a HOLD typically due to no CIP return flow which is measured at the CIP skid. Diaphragm failures can be found through the pressurization and venting of individual flow paths. Pathways that are blocked will not vent properly.

On-line Testing and Calibration Issues

On-line sample testing is currently available for conductivity and TOC assays. The benefits of using on-line measurements versus grab samples are the minimization of sample contamination, continuous on-line measurement availability, reduction of laboratory costs, decreased glassware use, and decreased variability.[10]

The final rinse conductivity is a typical acceptance criterion specified in the CV program and also should be the target utilized for CIP CD. The FDA's *Guide To Inspections Validation of Cleaning Processes* states that,

> *"Check to see that a direct measurement of the residue or contaminant has been made for the rinse water when it is used to validate the cleaning process. For example, it is not acceptable to simply test rinse water for water quality (does it meet compendia tests) rather than test it for potential contaminants."*[11]

The final rinse conductivity specification needs to be correlated to acceptable levels of detergents and/or process residues to be a meaningful value. Most CIP skids utilize a conductivity sensor that is mounted on the CIPR header. Conductivity is a function of temperature and the sensor may utilize configurable temperature compensation algorithms. The calibration method should be appropriate for the temperature compensation configuration and both the calibration and compensation are in alignment with the CV acceptance criteria. For example, one conductivity sensor vendor offers several compensation settings for high purity water applications: 2%/°C linear, ASTM 5391, or non-temperature compensated.

On-line TOC analyzers are becoming available for Water-For-Injection (WFI) and Purified Water (PW) systems although applications for CIP use are not as common.[12] Addressing these issues during the CIP CD program may minimize the need to obtain grab samples CV.

CIP CD Automation Issues

Holds, Stops, and Aborts

One purpose of CIP CD is to identify and eliminate the cause of HOLD, STOP, and ABORT states used in automated CIP cycles. CIP cycles have the ability to be placed into one of these states due to a critical process alarm or condition. During normal operations (post CV), a limited number of RESTARTS is generally permitted because the CIP cycle step will be repeated, thus delivering more than the minimum cleaning regiment. A critical question might be: are data gathered from a CIP cycle that experiences a RESTART acceptable for CIP CD or CV? If the efficacy of the restarted CIP cycle is not equivalent to a normal CIP, the answer is probably "No," because the extended cycle being tested does

not represent worst case. A determination of when RESTARTS are permitted for CV requires input from the CIP CD team, validation, engineering, and quality.

CIP CD Data Management

For a large scale biotech facility, the amount of data accumulated during a CIP CD program can be prodigious when rinse and swab samples are taken. The CIP CD and CV programs may require rinse sampling for TOC, conductivity, pH, bioburden, and endotoxin, and swab samples for TOC and bioburden. It is not unusual to have on the order of 50 to 100 CIP circuits within the project scope. Sampling each of these circuits for the required assays can produce thousands of data points which need to be analyzed and correlated to other factors such as: batch ID, equipment ID, CIP circuit ID, CIP start time, CIP end time, soil type, dirty hold time, clean hold time, sampler, sample date and time, sample location, visual inspection status, RESTART status, and analytical result acceptance limits. Utilizing a database to track these inputs allows the CD team to produce reports that can be used to assess the efficacy and robustness of the CIP cycles. In addition, the database can be used to track CIP cycle failure investigations and values of recipe configurable parameters. It is not unusual to have the need to specify and track thousands of configurable parameters which is difficult using a simple spreadsheet.

CIP CD Soiled Testing Issues

Clean Hold Time

Most CV programs specify a Clean-Hold-Time (CHT) testing requirement. CHT is a validated time the equipment can remain out of service in a clean state before the equipment must be re-cleaned prior to use. Equipment that is left in a dry state will have a decreased risk of failing CHT validation because of low bioburden loads The typical CIP cycle will end with an air blow step to remove excess water and dry the equipment or piping surface. The length of the final air blow may need to be longer than intermediate air blows to achieve the required level of dryness. Following the final air blow, small droplets adhering to the side-wall are usually acceptable. Leaving the vessel in a pressurized state at the end of the cycle should inhibit the ingress of microbial contaminants, but poses a risk to personnel requiring equipment access. The CD team should determine the proper state that the equipment should remain in at the end of a CIP cycle. Other means of microbial ingress should be evaluated for each unit operation.[13]

Dirty Hold Time

CV programs should include definition of the Dirty-Hold-Time (DHT) validation strategy. During DHT testing, a piece of equipment is soiled and quarantined for a specified hold period.

> *"The time duration for the stationing of soiled equipment must be optimal for the survival of bioburden in a physiological state to survive subsequent cleaning. As soiled equipment dries, the solute concentration increases with attendant reduction in water activity. It is well established that with low environmental water activity that microorganisms lose viability; during equipment drying the surface borne bioburden will similarly lose viability, such that upon complete loss of water there is an overall reduction in bioburden. Furthermore, the surviving population of microorganisms will not be in the optimal physiological state to survive or advantage subsequent cleaning process. Worst-case dirty hold time is highly dependent upon the duration of equipment drying."*[14]

Conducting dirty hold testing during soiled CIP CD will mitigate the risk of failures encountered during CV by determining the worst case hold time based on maximum viable bioburden load and/or dried residue. The worst case DHT in terms of bioburden load may not be defined by a dry piece of equipment.

Practical Rinse Sample Concerns

Most firms have SOPs which describe the rinse sample technique, containers to be used, and subsequent sample handling and processing. However, biotechnology manufacturing equipment and piping is often not designed with a permanent sample port needed for CIP CD and CV programs. The CIP CD team should identify all rinse sample locations and ensure that samples are obtained and handled in a manner which ensures that it is representative of the stream being sampled. The sample procedure should include flushing of the sample port prior to obtaining the sample.

Practical Swab Sample Concerns

Definition of a swab site matrix and the swab strategy is essential to effectively planning a CIP CD program. Swab sampling is intended to capture surface data from a variety of product contact materials that are representative of hard-to-clean and easy-to-clean sites. The definition of these locations should be based on the equipment configuration and the cleaning method employed. The use of PIDs, mechanical drawings, and/or equipment walk-downs is recommended for identifying these locations. CIP CD data can be used to quantify where hard-to-clean sites are located. The CV program then might be narrowed to a more limited regiment of locations. Gaining access to swab locations can be challenging and may require confined space entry, equipment disassembly, or the use of a swabbing pole. If a swabbing pole is used, the qualified swabbing technique should account its use.

Visual Inspection Issues

With respect to cleaning procedures, 21 CFR Part 211.67 (6) states the following:

> *"These procedures shall include, but are not necessarily limited to, the following: Inspection of equipment for cleanliness immediately before use."*[15]

Firms should have a visual inspection requirement integrated into the overall CV program to comply with good manufacturing practices. It also has been documented that in certain applications, visual inspection may be the only neces-

sary acceptance criteria for equipment CV.[16]

In any case, it is advantageous to begin the visual inspection process during the soiled testing step of CIP CD. A Visual Inspection SOP should be used to define what is deemed an "acceptable" visual inspection. However, in general, equipment which fails a visual inspection can exhibit streaks or spots of residue, a general haziness of the surface finish, and/or undrained rinse water. The visual inspection is one method to determine if an acid wash demineralization step is necessary as a typical part of a CIP cycle. Certain intermediates, products, and detergents themselves may have a tendency to cause the build-up of an inorganic residue layer on the vessel and piping. This can be mitigated through the use of a demineralization step. Including an acid wash step will increase CIP cycle times, but may be the only way to prevent mineral and/or rouge build up on stainless steel surfaces.

Derouge Issues

Rouge has been defined as:

> *"...an iron oxide film that forms on the surface of stainless steel with the industrial use of distilled and high purity water... It is a form of superficial corrosion that goes unnoticed and unreported in most industries, but is a major problem wherever exceptional cleanliness is required."*[17]

The most efficient method to control rouge is the specification of materials of construction that will be highly resistant to rouge formation. Nonetheless, practical experience has shown that rouge may start to become visible during the start-up process as equipment comes into contact with high purity water and other oxidative processes such as Steam-In-Place (SIP) cycles. Rouge removal can be accomplished as a periodic maintenance activity. The CIP chemical vendor typically can provide recommendations for CIP chemistry that are specific for derouge applications. Concentrations are typically much higher and exposure times significantly longer than a normal CIP. The derouge cycle can place an increased burden on manufacturing production in terms of cycle times and produce a significant amount of concentrated chemical waste. The CD team will need to assess if enabling a normal acid wash during a CIP cycle is more advantageous than a derouge CIP cycle run as part of a preventative maintenance program.

CIP CD Process Improvements

Successfully completing a CIP CD program requires planning and good project management practices. It involves time and resources during the start-up schedule; and therefore, adding cost to the overall project. Is this cost and effort justified? The following examples are a few of many qualitative approximations of efficiencies gained.

Water Use Minimization During Wash Steps

Optimizing wash volumes will reduce the amount of water usage. For a facility that has 100 CIP circuits with an average CIP circuit hold-up volume of 200L, the following approximates the water savings:

Assumptions

1. 100 CIP circuits are used to clean all equipment and transfer lines twice a month.
2. The average hold-up volume of all circuits is 200L.
3. The optimized wash volume is 250L developed during CIP CD.
4. The non-optimized average wash volume would have been 400L based on using maximum working volume of the wash tank.
5. The facility uses a caustic and acid wash for all CIP cycles.

100 CIP circuits × 2 cycles/month × 12months × (400L-250L) × 2 washes/cycle = 720,000 L/year of water savings.
Assume a nominal chemical concentration of 1% by volume for caustic and acid washes.
720, 000L × 1% = 7,200L of chemical additives not used.
Total volumetric waste savings = 720,000L + 7,200L = 727,200 L/year.

Optimized CIP Cycle Times

It is not uncommon for a caustic/acid CIP cycle to take on the order of two to four hours when optimized. If the CIP CD program achieves a 20% improvement in cycle time efficiency (by addressing the issues outlined above) than would have otherwise been implemented, the following might apply.

Assumptions

1. 100 CIP circuits are used to clean all equipment and transfer lines twice a month.
2. The average optimized CIP cycle takes 2.0 hours.
3. The average non-optimized CIP cycle would have taken 2.5 hours.

100 CIP circuits × 2 cycles/month × 12 months × 0.5 hours = 1,200 hours of production/year.

Selective Enabling of Acid Wash

As stated above, the CIP CD program can be used to identify equipment that is at risk for inorganic residue deposition during production. Such equipment is a candidate for a PM derouge cycle or a CIP cycle configured with a dilute acid wash. If the equipment utilizing the acid wash does not need to be derouged, the following might apply.

Assumptions

1. 50 of 100 CIP circuits exhibit a tendency to form inorganic residue films after use.
2. The 50 circuits without an acid wash need to be derouged twice a year.
3. The derouge cycle requires 20 times the normal acid wash concentration (10% by volume as opposed to 0.5%) and takes 6 hours.
4. The normal CIP cycle with the acid wash enabled takes an additional hour.

50 CIP circuits × 2 cycles/year × 6 hours = 600 hours of additional PM cycles.

50 CIP circuits × 2 cycles/month × 12 months × 1 hour = 1,200 hours of acid wash time.
1,200 - 600 = 600 hours of saved production time by using PM cycles.

However, this time savings must be balanced against increased chemical usage.

50 CIP circuits × 2 cycles/month × 12 months × 250L x 0.5% = 1,500 L used for wash.
50 CIP circuits × 2 cycles/year × 250L × 10.0% = 2,500 L used for PM cycles.

The benefit of 600 hours of saved production time needs to be weighed against increased waste discharges of 1,000L of acid chemicals.

Grouping of Parallel Paths

Bioreactors are designed with multiple inlet ports and other pathways that are cleaned with the vessel. These include media inlet, inoculation, acid, base, vents, overlay, sparge, and sample lines. The valve cycling composite controls the opening and closing of these pathways while providing flow to the sprayball and typically includes 10-15 individual flow paths.

Assumptions
1. Bioreactor has 15 parallel paths that are cleaned including the sprayball.
2. The sprayball exposure time = 10 minutes and each parallel path = 2 minutes for each rinse and wash.
3. The non-optimized valve cycling composite opens each pathway sequentially.
4. The optimized valve cycling composite groups the paths into five "families," while ensuring that each branch is turbulent.
5. The CIP cycle includes five steps: pre-rinse, caustic wash, intermediate rinse, acid wash, pre-final rinse, and final rinse.

Non-Optimized: 10 min + (15 × 2 min) = 40 min
Optimized: 10 min + (5 × 2 min) = 20 min

Optimized CIP Cycle Time Savings: 5 × (40 - 20) = 100 minutes/cycle.
2 cycles/month × 12 months/year × 100 min = 2,400 min = 40 hr/year production time/reactor

Optimizing Gravity Drains and Air Blow Times

Gravity drains and air blows are utilized to clear the circuit of wash and rinse solutions in an efficient manner. The optimal times need to be verified by visual inspection at the point where the circuit is piped to drain and/or by utilizing the CIPR flow switch.

Assumptions
1. 100 CIP circuits that utilize the five step CIP defined above
2. Each rinse is divided into two parts which gives the CIP cycle a total of eight steps utilizing gravity drains and air blows (GD/AB).
3. The average optimized combined GD/AB step is five minutes and the non-optimized would have been seven minutes.

100 circuits × 2 circuits/month × 12 months × (7 to 5minutes) × 8 CIP steps = 38,400 minutes = 640 hr/year

Conclusion

CIP CD is an activity that can be incorporated into the overall start-up schedule of a biotechnology manufacturing facility provided it is well planned and managed. The activity provides an opportunity to apply the concepts of QRM to a critical manufacturing process. CIP cycles can be configured to run in a robust and efficient manner. Costly CV failure investigations can be minimized. All the manufacturing facility stakeholders benefit from implementing such a program, including most importantly, the patient.

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The Role of Process Simulation in a Renovated Biologics Facility – A Case Study

by Daniel Lavin, Himabindu Gopisetti, and Peter N. Notwick, Jr.

This article describes the application of standard process simulation techniques to predict the performance of an existing biologics plant after recent upgrades of the facility. The work confirmed the viability of the proposed design, but with qualifications.

Introduction

Process simulation is a well-established practice in the biopharmaceutical industry that has been applied extensively to all types of biologics capital projects. Simulation is used to guide the design of major grassroots facilities and incremental expansions as well as for production scheduling, planning and optimization of operations in existing facilities.

The universal demand for process simulation has spawned a number of solution methods as well as solution providers. Both homegrown and commercially available software tools have been developed and used with varying degrees of success. As might be expected, the simulation tools vary widely in capability and applicability. Some are globally adaptable to nearly any sort of problem, while others were developed to model one particular type of facility or system. Most privately developed simulators are spreadsheet based, while the commercial software packages frequently use a database platform.

The primary question that process simulation attempts to address is the number and size of production and support resources that are required to meet the manufacturing goals of the plant. This article describes a somewhat unusual case study that illustrates one more

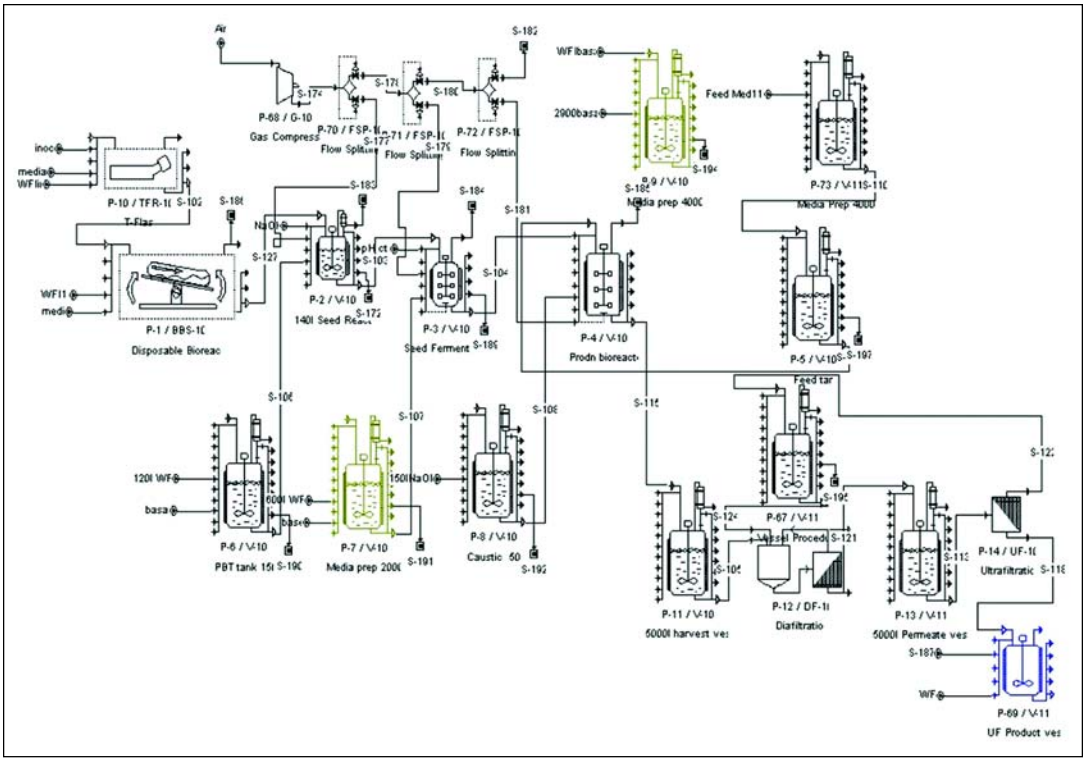

Figure 1. Schematic of upstream process.

aspect of the applicability of modeling to biologics plant problem-solving.

Background

In this study, a clinical manufacturing facility operated by a major pharmaceutical manufacturer was being pressed into service as the commercial launch facility for a new product. The original plant had been designed to be used as a non-GMP development facility. Over the years, it had been expanded and upgraded incrementally to produce clinical trial material. To accomplish its new mission, the facility had recently undergone upgrades to bring it into full compliance with cGMPs prior to the FDA Pre-Approval Inspection (PAI) for licensing.

Due to the strategic criticality of manufacturing sufficient quantities of the new product, the management of the facility wanted a high level of confidence that they could meet their objectives. Chief among their concerns was whether or not the non-personnel resources (primarily process systems capacity and utility supplies) were sufficient to support the target production rate. This requirement was reduced to two questions:

- Can the process systems produce the target annual amount of product?
- Do the clean utility systems have sufficient capacity to support production?

The Problem

Due to the incremental nature of past facility expansions, the production and support systems were neither integrated nor symmetrical. The configuration of the plant included:

- a cell culture operation that included four seed trains that feed six 5000L production bioreactors
- two identical cell separation trains
- three purification trains, each with four chromatography columns and two UF/DF steps, as well as its own dedicated buffer prep and hold
- four purified water generating trains whose distribution system feeds the WFI and clean steam generators
- three WFI stills of various capacities
- two non-overlapping WFI distribution systems

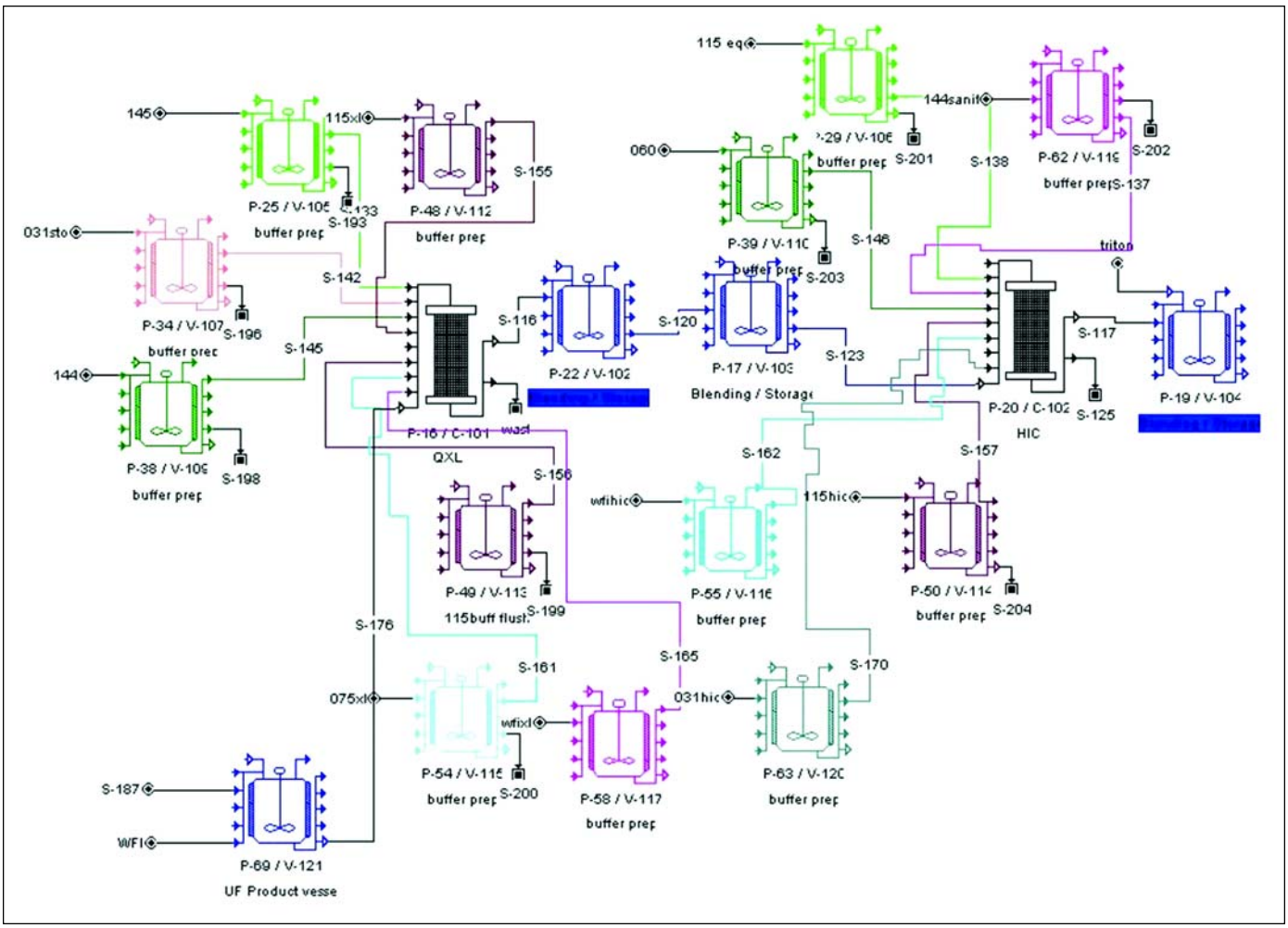

Figure 2. Schematic of downstream process (partial).

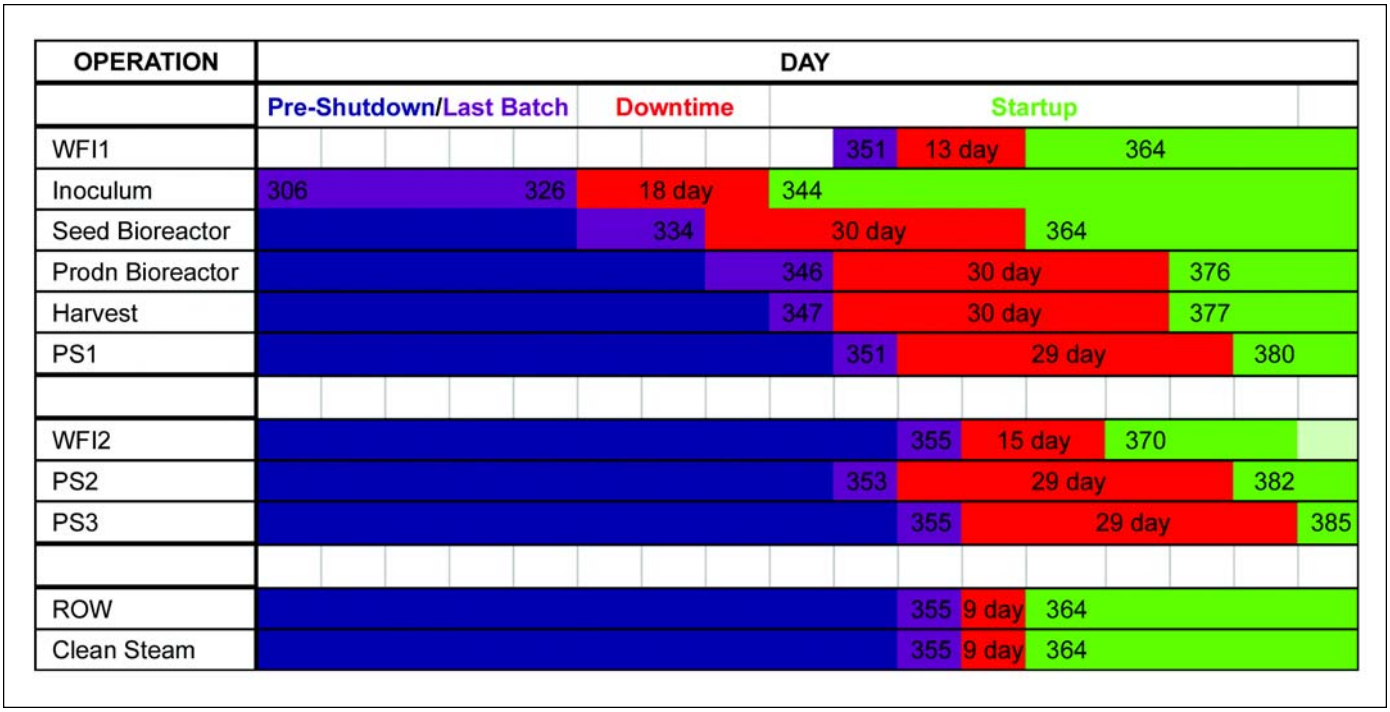

Figure 3. Rolling shut-down and start-up sequence.

- one clean steam generator

One significant advantage was that the simulation would use as its "model" a process that had been operated extensively in the plant at scale. Therefore, reliable data existed not only for the process parameters, but also for the actual cycle times that had been achieved. As a result, the expectation was that this simulation would be "realistic" (i.e., highly reliable).

The primary specifications or production basis that set the ground rules for the analysis consisted of:

On-Stream: Each process system operates 351 days per year. Note that the scheduled shutdown of individual operating areas would be staggered in order to maximize productivity, resulting in an annual "rolling" shutdown.

- SIP initial heat up period is 5 minutes for small equipment, 10 minutes for vessels $\leq$ 1000L.
- SIP hold times are 50 minutes at sterilization temperature.
- Autoclaves and glass-washers are operated exclusively during the day shift; each unit is operated 3 times per day.
- Net water consumption of each glass washer is 100 gallons per cycle and each cycle lasts 15 minutes.
- POU heat exchangers are steamed and flushed once per day. Cold flushes occur once per hour on idle units.
- WFI and RO water tanks call for make up at 75% and continue filling until they reach 100% working volume

Table A. Example of rules-based operating parameters.

Maintenance Shutdown: 14 days of shutdown per system per year. Due to the long start-up and shut-down sequences, all systems would not be in a "cold" shutdown state at the same time.

Cell Culture Batch Size and Titer: Typical for this sort of manufacturing process.

Production Bioreactor Cycle Time: 15 days average from inoculation of one batch to inoculation of the next batch (i.e., includes cleaning, steaming, and preparation).

Production Bioreactor Success Rate: 90%

Cell Separation Recovery: 85% based on assumed cell culture yield

Purification (Downstream) Yield: 43% based on assumed cell culture yield

As anyone familiar with the operation of biologics plants knows, these specified parameters are only averages. In practice, even the best characterized and controlled process experiences "normal variability" in its performance. For instance, the time required for the production bioreactor to achieve its target titer can vary by two days from the average. In addition, there is an acceptable band of variation in final titer that triggers the decision to harvest. Similar tolerances exist for all of the process operations.

Recognizing this, the manufacturing management was not satisfied with a "snap-shot" of the facility performance that considered only the average case. Rather they required

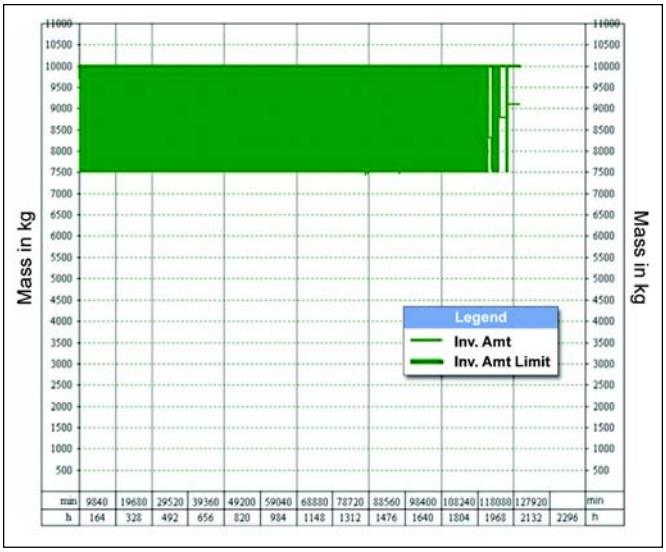

Figure 4. WFI inventory for multiple batches.

the analysis of certain key parameters to determine the effect of their normal variability on operations and productivity over the long term.

Approach

The two primary aspects of process simulation are the strategy and the tools.

Strategy

Most simulation strategies require that a base "static" (i.e., deterministic) model be developed. The model at this stage strings together all of the unit operations of the production and support systems into an integrated whole. The static model is usually based on the average performance scenario.

This base model serves as a template for the available operating data. In the process of using the data to build and debug the model, deficiencies in that data come to light, which must be addressed by supplying additional data or by applying reasonable assumptions. Eventually, this process results in a complete, coherent, functioning representation of the operating systems. Therefore, regardless of the ultimate objective of the simulation exercise, the development of the static model is an essential first step in reaching the overall objectives.

Tools

In this case study, the manufacturing user group recommended the particular suite of simulation software that was used. Unfortunately, one of the limitations of this software at the time we used it was the fact that it could accommodate only a "single train" process, i.e., one bioreactor train and one purification train. This was obviously not suitable for the plant configuration that was being simulated. However, once the single train model has been developed, its results can be downloaded into a companion application. The latter process scheduling tool can accommodate multiple trains in the asymmetric configuration of the actual plant. It also can simulate the sharing of common resources and provide an overall schedule of events, identifying bottlenecks.

The net result was that the first step of the model development process actually consisted of two steps: the development of the single train model followed by the preparation of the multi-train resource scheduling model.

When the static resource scheduling model had been exercised sufficiently to demonstrate that there were no limitations in the average performance case, the remaining task was to test the effects of the variability of the major process parameters with a dynamic (stochastic) simulation. In this type of simulation, the target parameters are allowed to vary between limits based on a normal (symmetrical) or skewed (asymmetrical) distribution around each parameter's average. The Monte Carlo method is the most popular statistical analysis tool for this purpose. For this dynamic simulation study, Decisioneering's Monte Carlo-based Crystal Ball software was chosen.

Single Train Static Model

One of the most challenging aspects of this component was data gathering and conditioning. This is due in large measure to the sheer volume of detailed information that is required by the software to simulate each unit operation.

Gathering some of the information was relatively straightforward because certain items could be stated succinctly. Rules laid down for clean utility usage or CIP and SIP treatment parameters fell into this category. Table A gives examples of these operating rules.

Determining the values of actual process parameters was more problematic. While it was generally true that the process operating in the context of this particular plant was well known, the detailed operational information was not readily accessible to the modelers. The data was primarily contained within completed batch records that had to be obtained and then "mined" for the desired information. The manufacturing user group provided a summary of the typical values for the measured process parameters. However, obtaining the typical durations and utility consumptions of the individual steps of the various CIP and SIP cycles required particular effort because these are not tracked by manufacturing operations.

Although the single train model was only the first step in the development of a static model that simulated the clinical manufacturing facility, it did yield some results that progressed the study and indicated a favorable ultimate outcome. Some of the salient results were:

- The calculated yield per batch of finished product was reconciled with actual plant operating experience. This was a check on the consistency of the performance data supplied for the individual operations.

- The duration of virtually all high rate WFI demand episodes was less than 15 minutes. Only one type of WFI demand was found to have a long duration (60 minutes) at high rate. This meant that the generators had frequent and sustained opportunities to replace used volume.

- No WFI demand rate exceeded the generation rate, an indication that the WFI surge vessel's capacity would not be taxed. In fact, the level of the vessel never fell below 75% – the point at which the generator is turned on.

Figures 1 and 2 present some of the graphical output that facilitated debugging by permitting a visual confirmation of correct connectivity among the process systems.

Static Resource Scheduling Model

With the data vetted and the single train model accurately simulating the process, the data for individual unit operations were loaded into the process scheduling tool. Here, parallel operations could be propagated to represent the actual plant configuration. This included the ability to represent multiple sources of WFI; the key study resource.

An important aspect of the WFI system was that the three generators overlapped their duties by being able to supply either of the two storage and distribution systems. The actual operating scheme dedicated one still to each of the two storage and distribution systems with the third (largest) still as a common backup. However, recall that the user populations of the two storage and distribution systems did not overlap so the two systems could not back-up each other. In practice, the plant's control system could direct the output of the common backup still to either of the storage and distribution systems based on perceived need. However, the software did not permit a rule-based allocation of WFI still output in this way. The work-around was to permanently apportion the backup still's output between the two users. The results of the single train model provided the guidance for this selection.

The lack of modules that could be used to represent clean steam and WFI stills (with their attendant blow down and start-up requirements) was addressed by treating these as point sources with no attributes. This necessitated that the evaluation of the adequacy of the primary water treatment system be carried out by manual calculation of primary water demand, adding the consumption of these generators.

Another manual intervention was the inclusion of the bioreactor success rate. There was no provision in the software to accommodate the rule that approximately 10% of the batches are expected to fail over time for various reasons. However, it was a simple matter to determine the required success rate from the number of batches that the model predicted could be produced in a year.

When the static resource scheduling model was debugged and ready for use, it was used to simulate operation over increasingly longer time periods. This permitted analysis of the model output to determine whether there was a gradual accumulation of systemic errors in the model. Finally, the resource scheduling model was run for a period simulating a two year operation, including the annual rolling shutdown.

The rolling shutdown is a feature peculiar to commercial scale cell culture plant operation schedules. A brief consideration of the nature of a cell culture-based biologics facility makes obvious why this type of shutdown is required.

Consider that the purification of a batch of crude, harvested product requires approximately 7.5 days. Thus, by the time the last batch before a shutdown has been cleared from purification (i.e., filled), the bioreactor that produced it has been idle for 7.5 days. The bioreactor that produced the previous batch has been idle for 2.5 days longer than that, etc. So by the time the last batch has been purified and filled, the first bioreactor to be idled has been empty for almost three weeks. Moreover, the inoculum lab and the seed bioreactor trains have been down longer than that. Therefore, in order to maximize productivity, the front end operations should be undergoing maintenance while the last batches of product are being purified.

This staggered shutdown has to be performed in reverse during startup. The inoculum lab must be in operation 20 days before the cell culture is grown up sufficiently to inoculate the first seed reactor. An additional 23 days must elapse before the first batch of cell culture is ready for purification. This is ample time to conduct the annual maintenance program on the downstream portion of the plant and return it to readiness.

The primary complication is that the clean utility systems, which are an indispensable part of these operations, also require annual maintenance. If only one generation and distribution system of each type is available for the entire facility, it would not be possible to perform a true rolling shutdown. At some point, the entire plant would have to be idled while the utility systems are serviced. The usual practice in designing a new plant is to provide separate, dedicated utility systems for the upstream and the downstream. In that way, the utility systems can be maintained while the corresponding section of the plant is down. The caveat is that the dedicated clean utility system for a given area of the facility has to be the last system shut down and first system returned to service.

Returning to the timelines described above, it turned out that the inoculum lab must be returned to service before the WFI system that supplies it can be shut down for maintenance. In a new plant, this is often handled by providing a

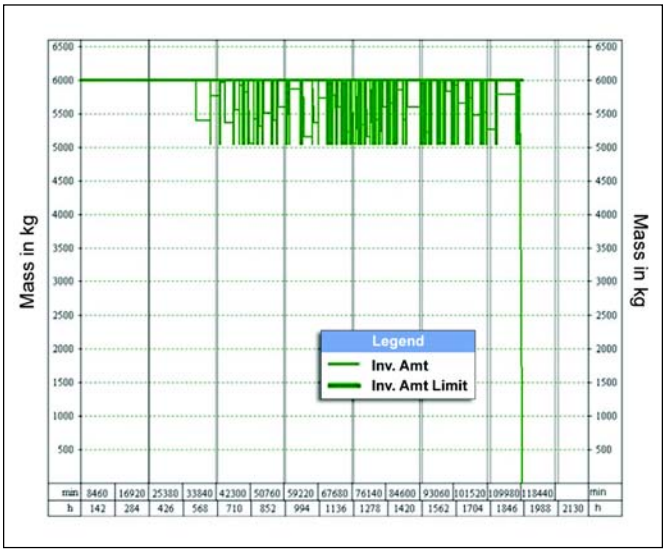

Figure 5. RO water inventory for multiple batches.

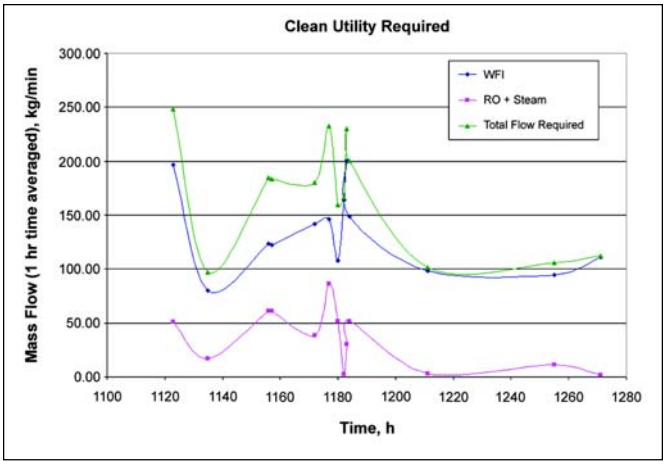

Figure 6. Plot showing the utility usage over a certain period of time.

cross-tie that allows the early restart systems such as the inoculum lab to be supplied with WFI from the downstream WFI system which is still in operation at that point. In an operating plant, adding that provision can prove challenging because of the downtime required to install, qualify, and validate the new cross-over piping.

The target of 14 days shut down for each system is by no means rigorous. Figure 3 presents the actual results from the simulation of the rolling shutdown for this case. It will be noted that the shutdown of certain systems is actually shorter than 14 days while for many systems the shutdown is much longer. This is the natural result of the interplay of the cycle times, the sequence of operations, and the configuration of the plant.

Results of the Scheduled Resource Static Model

The static resource scheduling model did confirm that the target production could be met with the plant as currently configured. However, there were a few qualifications.

- The 14 day shutdown target could not be met for some systems. The cell culture WFI system could tolerate only a 13 day shutdown. More importantly, the primary water treatment system could be down for only nine days. Likewise the allowable outage for the clean steam generator was only nine days. In grassroots designs, these sorts of conflicts are addressed by adding redundancy to the generation systems and cross-ties to the distribution systems. For existing plants, other remedies must be sought. In this case, the one day WFI system shortfall was deemed not to be a problem. The primary water treatment system actually consists of four trains. Maintenance work on these could be staggered so that the nine day outage, (which is required only for the storage and distribution portion of the system) could be adequate. Clean steam could be sourced from a unit in an adjacent plant that has an independent water supply and is cross-tied to the distribution system serving this facility.
- The requirement for WFI in order to maintain operation of the inoculum prep lab during start-up while both WFI systems are shut down can be met with bottled WFI, which can be obtained commercially.
- The bioreactor batch success rate would have to reach 94% instead of the target 90% rate.

Aside from those qualifications, the simulation predicted that the facility's resources were adequate to meet the production targets as follows:

- Overall, clean utility capacity is more than adequate.
- The instantaneous WFI demand never exceeds the total generation capacity of the available stills.
- Neither the primary water surge nor the WFI water surge ever fall below the 75% "refill" level - *Figures 4 and 5*.
- The downstream processing capacity is not limiting production.

Since the combined clean utility capacity cannot be obtained directly from the static model, the individual consumption data for Reverse Osmosis (RO) water, clean steam, and WFI for a selected high demand period of time were loaded into a spreadsheet. The plot generated by this application shows that at any point in time, the total demand of the clean utilities does not exceed the overall generation capacity - *Figure 6*.

Finally, the multiple year run of the static resource schedule simulation confirmed that there were no subtle effects that would eventually prevent production of the required number of batches in a given year.

The Monte Carlo Dynamic Simulation

In order to analyze the effect of the normal variability of process and operating parameters on production, a Monte Carlo simulation was carried out. However, due to software compatibility issues, the static process resource scheduling model could not be directly linked to the dynamic model. Therefore, a separate model was developed utilizing the results from the static process model as inputs to a spreadsheet. In this way, a simplified system of six bioreactors and three purification suites was simulated.

The variables and their selected ranges reflect the "normal" variation in cycle times in the process. The variables selected for this sensitivity analysis are production bioreactor cycle time and purification process batch cycle time.

The following specifications were selected for this study:

- A new batch is harvested from one of the six bioreactors at an average interval of 2.5 days.
- The cycle time of each bioreactor varies between 13 to 17 days with the most likely cycle at 15 days.

- The cycle time to complete purification of a batch was specified to be in the range of six to 7.5 days with the most likely duration at seven days. The reason for choosing 7.5 days as the maximum limit for the purification cycle time was to match the average bioreactor batch cycle time (this also was the basis for the static model). In fact, the detailed results from the static model showed that much shorter purification cycle times were possible.

Results of the Dynamic Simulation

The dynamic sensitivity analysis was carried out for two cases: production for a period simulating a one year operation and production of 1000 batches. The latter, which represents more than eight years of operation, was chosen arbitrarily as a time sufficiently long to expose any subtle long term trends. The model output for the 1000 batch case had a slightly higher negative skew than the output for the one year case - *Table B*. This higher negative skew is due to the specification of the purification batch time ranging from -1 to + 0.5 day around the most likely cycle time of seven days. This seven day period was derived from the study of individual downstream unit cycle times using the static model. While the average cycle time and variability of the production cell culture was well known, at the time of this study, the facility was not staffed to maintain round-the-clock operations. Consequently, the achievable purification cycle time had not been demonstrated. Therefore, some prudent judgment had to be exercised concerning the average cycle time as well as the variability for downstream processing.

The result reported is the combined effect of varying the cycle times of both the production bioreactors and the batch purification process. Due in part to the selection of an asymmetric variation in downstream cycle time, more early batches (hence, higher production rate) is indicated. This means that over time, the production limitation tends to shift from cell culture to purification operations.

The results suggest that if labor is not a limiting factor, then the production capacity of the plant can be increased slightly over time by the effective management of the purification suites' cycle times.

Conclusion

This process simulation confirmed that the upgraded facility had the capability to achieve the customer's production objectives with certain caveats. These qualifiers included such items as the need to provide WFI from a source outside of the plant for a short period of time after the inoculum lab is restarted and the need to sustain a 94% cell culture success rate instead of the proposed 90%.

More generally, the need to manage the expectations of the end user with regard to the delivery of results should not be overlooked when undertaking this type of project. It is always incumbent on the modeler to educate his customer that the preparation of a model requires significant time and effort on the order of man-weeks at a minimum. Even if the process input data is readily available, significant effort is required to condition the input, construct the model, enter the data, and then debug the model.

Forecast Name	1 year's batches	1000 batches
	Forecast	
Trials	1,000	1,000
Mean	0.02	0.64
Median	0.05	0.61
Standard Deviation	0.79	0.87
Skewness	-0.03	-0.08
Minimum	-1.87	-1.52
Maximum	1.93	2.84

Table B. Monte Carlo dynamic simulation results.

All computer models and simulations only approximate actual operations that take place in the real world. As such, the simulation output should be regarded as guidance rather than quantitatively precise predictors of future results. Depending on the sophistication of the end user, conveying this understanding also may present a challenge.

All other considerations aside, process simulation can and routinely does produce very useful results. Perhaps more importantly it provides excellent insights into the nature of the manufacturing operation, including what factors limit productivity and where the opportunities to streamline and optimize the process lie.

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Daniel Lavin has more than 17 years of biopharmaceutical process experience, which is evenly divided between biotech operating companies and engineering design firms. In his present position as Director, Biopharmaceutical Technology with Parsons, he designs cGMP processes and facilities and determines manufacturing strategies for many leading pharmaceutical companies. He has used process simulation to optimize the operations of existing facilities, and to design future facilities. In his previous positions at Genetics Institute (now Wyeth BioPharma) and Repligen, he developed, scaled up, transferred, and operated clinical production processes based on cell culture and microbial process technology. He has been active in ISPE for 10 years, serving on the Board of Directors and as President of the ISPE Boston Area Chapter.

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Robotic Processing in Barrier–Isolator Environments: A Life Cycle Cost Approach

by R.L. Dutton and J.S. Fox

This case study presents a Life Cycle Cost (LCC) analysis applied to an example of a roller bottle cell culture process that suggests how the process can be further optimized through a change in the process protocol.

Introduction

Since their introduction more than a decade ago, barrier-isolator systems have improved environmental control in aseptic and potent compound manufacturing. Barrier-isolator designs have improved over the years, and systems have been integrated into production lines in ways that would previously have been unimaginable.

The rapid adoption of barrier-isolators containing automation for continuous processes such as fill-finish is well documented.[1] The market for the technology in the potent compound environment is growing as well.

About 25% of all drugs currently under development are considered highly potent, i.e., those classified within Occupational Exposure Bands (OEBs) of three or more, compared to 5% to 10% of potent drugs currently on the market. This growth in hazardous liquids and solids will inevitably lead to greater use of barrier-isolators, and probably of automation within these mini-environments. It has been estimated that potent compound production is already responsible for up to 20 times the number of isolators used in fill finish operations.

Barrier-Isolators and cGMP

The advantage of mini-environments in pharmaceutical production is obvious. Not only do they minimize operator exposure but, when properly used, they minimize cross-contamination, aid in risk assessment, and lend themselves to redundant systems to avoid catastrophic events. In the case of potent compounds, it has been shown that a full isolator represents Personal Protective Equipment (PPE) that can be up to 10,000 times more effective than a fume hood, or 1000 times more effective than an air line full face pressure system.[2]

Recent FDA guidelines, and a 2002 FDA concept paper also support the advantages of isolators relative to conventional manual processes during aseptic production. The FDA and other regulatory agencies appear to be most comfortable with hard wall construction, positive pressure, high transfer integrity, chemically disinfected designs; especially when combined with good ergonomics and a well planned and strictly enforced operator training program.[3]

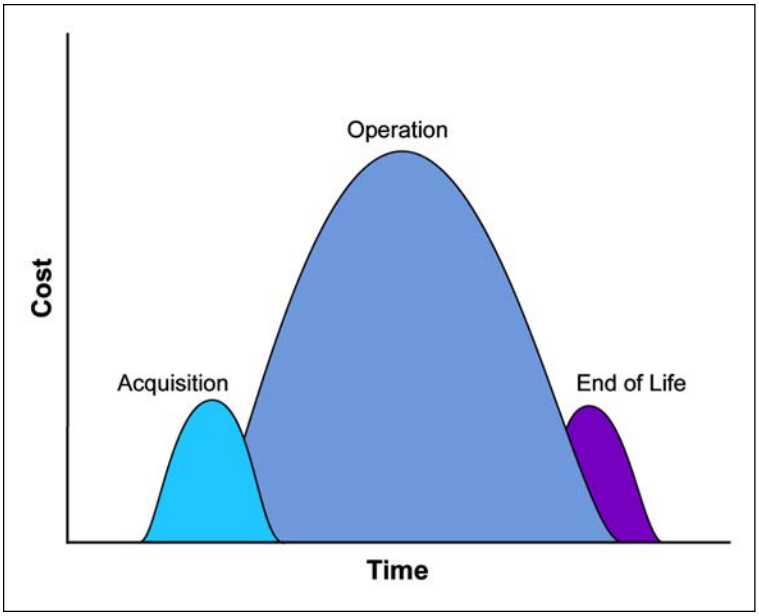

Figure 1. Acquisition cost for capital equipment commonly represents only a small fraction of its total life cycle cost. (Source: U.K. Office of Government Commerce)

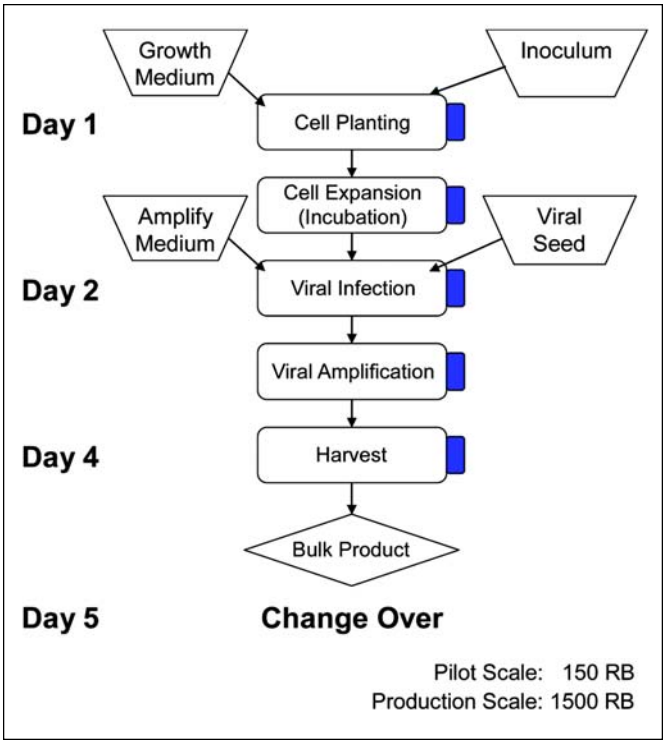

Figure 2. Typical aseptic roller bottle process flow for vaccine production, as well as typical roller bottle throughput rates per batch for pilot and production scales. Cell Expansion and Viral Amplification are incubation steps which represent significant wait times between manipulations during the process.

According to the FDA:

> *"Aseptic processing using isolation systems separates the external cleanroom environment from the aseptic processing line and minimizes its exposure to personnel. A well-designed positive pressure isolator, supported by adequate procedures for its maintenance, monitoring, and control, offers tangible advantages over traditional aseptic processing, including fewer opportunities for microbial contamination during processing."*[4]

All of this suggests that barrier-isolator use will continue to increase, and may even accelerate in the long term. Further, discrete robotic applications which minimize interaction through gloveports, may well represent the next significant advance in the technology. We note, in this regard, the current availability of washdown-compatible robotics and even robots compatible with automated vaporous hydrogen peroxide decontamination.

Although barrier-isolators make sense in terms of process contamination and operator safety, it has always been assumed that it inevitably makes economic sense. But are they a panacea for all aseptic (or, for that matter potent compound) processes?

Given the anticipated "boom" in barrier-isolator use, and particularly the probable appearance of many new discrete automation applications within isolation, it seems appropriate to re-examine the economic assumptions relating to the technology. In the following, one sample application is presented, roller bottle cell culture, while introducing a rigorous new financial tool – a life cycle cost model designed specifically for aseptic pharmaceuticals.

Introduction to Life Cycle Cost

Definition and Objectives

Life Cycle Costing (LCC) is a financial model that is commonly used to capture all of the elements of cost to produce a product over its total anticipated lifespan. In this article, we introduce LCC as a predictor of total cost over the service life of the capital equipment and building assets used to produce single or multiple products in the aseptic pharmaceutical environment.

In manufacturing, LCC is widely used as a decision support tool where management faces a choice of procurement and/or process layout options. The accuracy of LCC analysis diminishes as it projects further into the future so it is most valuable as a comparative tool when long term assumptions apply to all the options and consequently have the same impact.[5]

In summary, LCC is the discounted dollar cost of acquiring, operating, maintaining, and disposing of a piece of capital over a period of time. It can be defined as follows:

Life Cycle Cost = Acquisition costs + other capital costs associated with acquisition + recurring and non-recurring operating costs + direct and indirect support costs + disposal costs; where

- Acquisition costs = Product price = Product costs + selling, general and administrative + warranty costs + profit; where
  - product is the capital item
  - Product costs = Recurring production costs + non-recurring production costs allocated to the product
- Recurring operating cost = production labor + direct materials + process costs + overhead + outside processing
- Non-recurring operating costs = development costs + tooling

Value of LCC Analysis

The up-front or visible cost of most capital purchases in most manufacturing environments represent only a small fraction of overall life cycle costs. Its total cost is incurred throughout the life of an asset. Operating cost usually represents the largest cost element, but end-of-life costs also can be significant.

Purchase price may represent 15% to 25% or less in the area of production automation.[6] Yet the purchasing decision normally commits the user to much greater costs with very little scope to change these once the capital has been expended.

Given that in many pharmaceutical companies the capital purchase and operating funding come from different sources, there has been little incentive to use detailed LCC models for

purchasing decisions. Nevertheless, the values of its use are many, including:

- evaluation of competing options in purchasing
  - Options with the same purchase cost can have radically different life cycle costs.
  - Options with high purchase cost can result in significant savings on a total acquisition and operating cost basis, and vice versa.

- improved awareness of the total costs associated with capital expenditures
  - Using LCC, management can deconstruct and evaluate the elements of the factors contributing to a capital purchase, and hence, make better decisions.
  - Principle cost drivers can be identified, and these can become the drivers relating to purchase and production.

- modeling performance trade-off against life cycle cost
  - LCC allows purchase costs to be weighed against all production costs and efficiencies, i.e., it allows financial "what if" analysis, including sensitivity analysis over a wide variety of production parameters.

Therefore, LCC is an important risk mitigation tool which is very much in the spirit of the FDA's thrust toward "Risk-based GMPs." This is particularly the case when integrated with other models, such as process simulation.

LCC in Industry

LCC modeling has a history of use in construction, particularly as a tool for selecting the best investment options – new construction or retrofit. It also has been used in planning for reliability and maintenance for other complex engineering systems in defense, railway, aerospace, and other applications.

Whereas the focus in most cases has been on infrastructure, mature manufacturing industries also have begun to apply LCC to capital equipment. One example is automotive, where lean manufacturing processes include the balanced use of people, equipment, and material yielding the lowest life cycle cost. Lean equipment design is very much a part of this, causing suppliers to the industry to focus on LCC issues in upgrading their products to the extent of identifying guidelines for equipment design and providing a lean equipment checklist.[7]

LCC also has been used in semiconductor manufacturing to compare the cost of competing equipment technologies, without bias. One industry association sanctions a particular LCC model and has concluded that LCC analysis provides a valuable way to identify cost reductions, and has identified major cost elements of one particular generic wafer production process.[8]

LCC in Pharmaceuticals

LCC modeling is not new to the pharmaceutical industry. Traditionally, it has been used to determine economic risk related to infrastructure and facilities. Anecdotal evidence suggests that its use is growing for process equipment, but not necessarily for equipment in the aseptic environment. Models that we have seen are simple, capturing only acquisition costs (sometimes including cost of validation) and a small number of operating cost variables such as labor, utilities, and maintenance.

There is one pioneering effort to quantify the life cycle cost issues relating to barrier isolator fill-finish suites in relation to costs of the cleanrooms they supplant.[9] Porter clearly demonstrates the viability of the isolator barrier option on the basis of life cycle costing quantitatively with relation to facility vs. equipment size, cost, and energy consumption, and qualitatively on the basis of labor, and utilization levels. There also is another model focusing on potent compound applications.[2]

The following shows how we have built on Porter's effort by adding additional detail through acquisition, operating, and residual value-related parameters such as:

- environmental monitoring costs
- labor costs
- maintenance costs
- throughput
- system Overall Equipment Efficiency (OEE)
- cleaning and consumables
- QA/validation costs

Case Study

Developing a life cycle cost analysis for an aseptic pharmaceutical unit operation begins with understanding the process. Here, a detailed LCC model was developed for aseptic processing using an example taken from the upstream portion of a biopharmaceutical process. In a bioprocess, the culture step(s) that result in the bioproduction of the product are known as the "at stream" steps of the process. Here, the specific focus is on the "at stream" steps involved in the production of virus on animal cells in roller bottles.

A question immediately comes to mind – why roller bottles? Bioreactor technology is well developed with designs that address many diverse culture requirements. Nevertheless, roller bottles and T-flasks continue to find commercial application in animal cell and viral culture.

The decision to employ roller bottles at the commercial scale may be process or biology based. For example:

Figure 3. Typical automated roller bottle system for scaled-up production. The robotic arm is capable of handling approximately 1500 roller bottles per batch, based on a single shift per day.

- Roller bottles can be the culture vessel of choice for certain anchorage dependent, fastidious, or fragile animal cells, such as primary cells that are difficult to grow in the relatively harsh environment of a bioreactor.

- A product that can be manufactured from a small batch size may not warrant use of a bioreactor or the development of bioreactor protocols, such as the production of viruses on animal cells or many of the emerging cell and gene therapy products.

- In some cases, the use of micro-carriers for the growth of anchorage dependent animal cells in a bioreactor may prove problematic in either the culture portion of the process or in the downstream steps of the process.

There may be regulatory considerations involved in the use of roller bottles at the production scale. Production in roller bottles may have been established through their use in processing small volumes of pre-clinical and clinical material. Culture conditions may have been optimized in the roller bottle environment. Moving production from a roller bottle to a bioreactor is a major change in technology, and hence, in the process with attendant regulatory hurdles. In contrast, scale-up by an increase in the number of roller bottles is not considered to be a (major) process change. The investment required in implementing a major change to the process may not be warranted.

The At Stream Roller Bottle Process

A typical production of a virus on animal cells in roller bottles is depicted in Figure 2. The culture steps include inoculating the animal cell population into the roller bottles; allowing the cell population to grow (incubation); infecting the cell population with the virus; allowing the virus to amplify (grow) in the cells (incubation); and harvesting the product from the roller bottles. Inoculating, infecting, and harvesting procedures are active manipulations of the roller bottles.

When the roller bottle is the culture vessel, scale-up of the process is achieved by increasing the number of roller bottles. For example, a pilot scale process may use 150 roller bottles, while the production (commercial) scale may require 1500 roller bottles per lot. The number of days required for cell population expansion or for viral amplification may vary with the type of cell or virus or with the culture conditions. The lengthy incubation periods represent processing wait time during which there are no active manipulations of the roller bottles. Hence, this process negatively impacts overall equipment efficiency.

At Stream Roller Bottle Scale-Up Alternatives

Assessing the pros and cons of the scale-up alternatives can be a challenge. Typically, roller bottles are manipulated manually (i.e., inoculated, infected, harvested, etc.). A technical team is composed of a supervisor, one or two roller bottle handlers (technologists), an assistant, and an environmental monitor. In a typical process, a skilled technologist can handle 150 to 250 roller bottles per shift. As the scale increases, costly skilled technical labor becomes significant.

Unlike the closed system of the bioreactor, the roller bottles must be opened during each processing manipulation. When this is performed manually in a biohood, it is an open aseptic process, necessitating a Class A/B (Class 100 in Class 10000) environment. A Class B cleanroom is costly to construct, maintain, and monitor. Class B gowning is both costly and ergonomically unfavorable. As the scale increases, the cost of the facility increases.

Alternatives incorporate isolator technology, which inherently increases the quality by increasing the assurance of maintaining asepsis. A glovebox can be used in place of the open biohoods, but the ergonomics of manipulating roller bottles within a glovebox are even more unfavorable: the dexterity necessary to open and close roller bottle caps, add small volumes (e.g., 1 mL or less) to each roller bottle, swirl roller bottles, scrape cell layer of roller bottles, etc., is impeded by the bulky gloves and limited freedom of movement. Manipulation of the roller bottles can be automated and performed within an isolator. However, isolators and robotics carry a high capital cost. Also, a switch from manual to automated roller bottle handling may not be considered to be a minor change to the process.

The Economic Analysis – Equipment Capital Costs

In this case study, the manual process in biohood is compared with the use of a glovebox and with the automated process using a roller bottle handling robotic arm in isolator over an assumed system life of 10 years. The assumed system life, which is relatively short, reflects the likelihood of process and equipment improvements over time. Cellmate™ is a typical

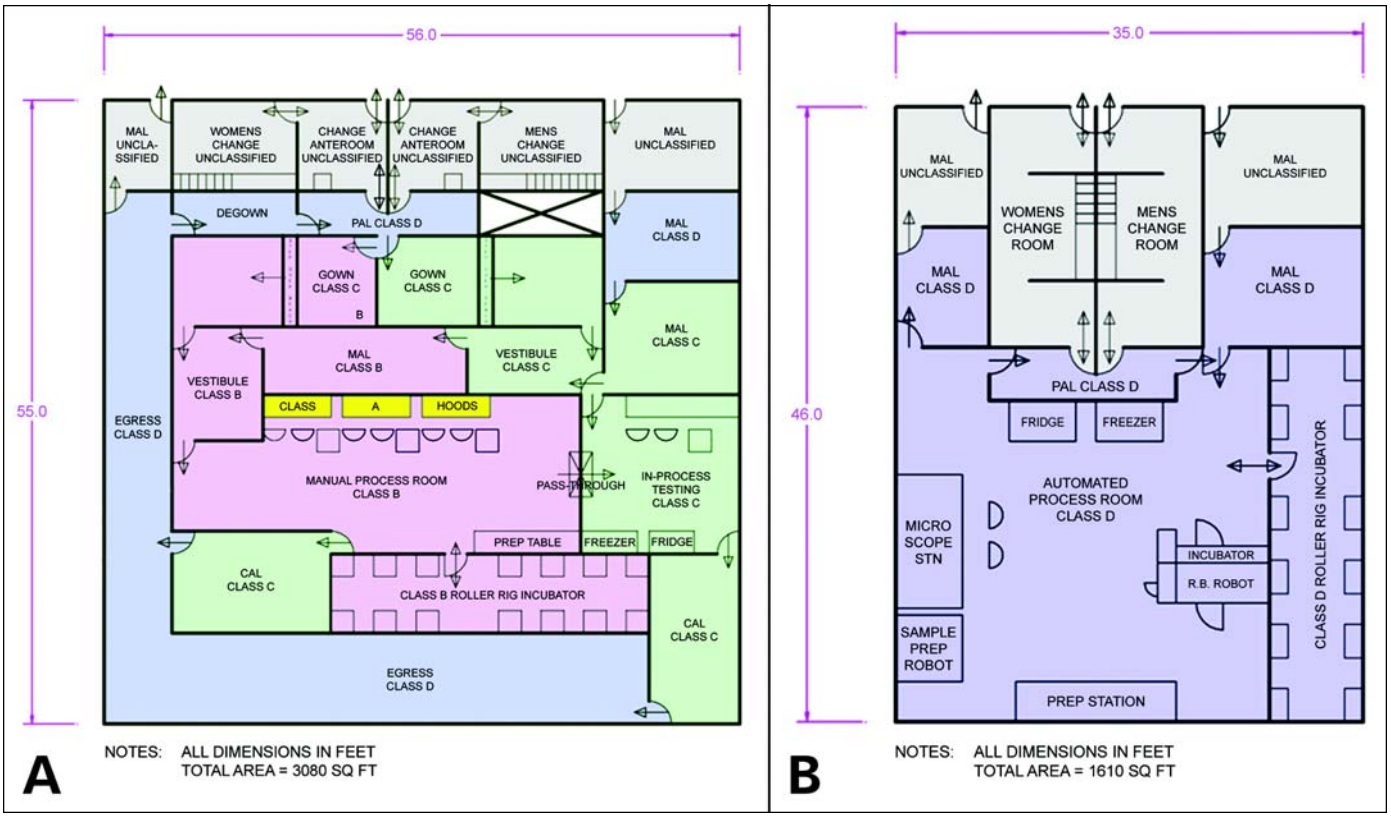

Figure 4: Comparative Infrastructures for a Class A/B aseptic processing environment for manual operations and a Class D environment suitable for an (automated) isolated roller bottle production system. MAL = material air lock; PAL = personnel air lock; CAL = combined air lock; U = unclassified.

automated roller bottle handling system that is manufactured by The Automation Partnership.[10] This roller bottle handling system incorporates a conveyor belt to move roller bottles to and from a robotic arm. The robotic arm moves the roller bottles to various stations within the isolator where manipulations occur. Manipulations include capping and decapping, inoculation, infection, medium addition, and removal, etc.

At the pilot scale (e.g., 150 roller bottles), the capital costs of equipment increase significantly from manual processing in an open biohood, through the glovebox option, to automated processing in an isolator (Table A, Line 1). The purely economic choice would seem to be obvious: compared with manual processing in an open biohood, the equipment for the glovebox option is more than six times more costly, while the robotics in isolator choice is more than 20 times more costly.

In a typical virus production process, a single robotic arm can handle on the order of up to 1500 roller bottles per batch. So as the process is scaled 10-fold from pilot to commercial production, no increase in the number of automated systems is required. In contrast, even with increasing the number of shifts per day, the number of biohoods or gloveboxes must be increased from one to three. Even so, on a basis purely of equipment costs, at production scale the glovebox and automation in barrier system options are seven to eight times more costly than the manual processing in open biohoods choice - *Table A, Line 10*.

Expanding the Economic Analysis – Facility Costs

The capital cost of the processing equipment is far from the whole LCC story. When the facility costs for the different options are considered, a different story emerges. The Class A/B aseptic processing environment requires a complicated and costly facility. Regulatory requirements for single classification step ups and step downs, and for separation of personnel and material flows, translate into multiple rooms and airlocks. Gowning requirements add further complexity and cost.

As depicted in Figure 4, the two isolator options require only a Class D background environment, which can be accommodated within a simple facility design that is much cheaper to maintain. At the production scale, the automation in isolator option requires only about half the square footage of the manual processing in open biohoods option.

Facility capital costs include both infrastructure and utilities capital costs. The utilities requirement to maintain the cleanroom environment is very costly, typically running higher than the infrastructure costs. For the manual processing in open biohoods option, the pilot scale facility for this example will run around $3.2 million (Table A, Lines 3 and 4); while the production scale facility will cost around $7 million (Table A, Lines 12 and 13). By comparison, the smaller, simpler, and lower cleanroom classification facility for the isolator options will cost only on the order of $1.5 million at

the pilot scale and $2 to $3 million at the production scale, depending on whether or not the process is automated.

When facility costs are added to equipment costs, there is much less difference between the three choices. However, with the additional consideration of ongoing environmental control and monitoring costs, the economic scales are tipped in favor of isolation at both the pilot and production scale for this roller bottle animal cell and viral based example - *Table A, Lines 6 and 15*. At the pilot scale, manual processing in gloveboxes is the cheaper option compared with automation in isolators; but at production scale, the costs for equipment plus facility infrastructure and ongoing environmental maintenance are more favorable for the automation in isolator option. When coupled with the ergonomic and quality benefits, the automation in barrier option is clearly the best choice at the production scale, and also may be at the pilot scale.

The choice at production scale can influence the choice at pilot scale. A change of equipment or a change to the process may result in interruptions to material supply, costly validations, and perhaps a requirement for bridging clinical trials. These are further cost considerations that have not been evaluated here.

Expanding the Economic Analysis – Validation Costs

The requirement for product quality is arguably more stringent in pharmaceuticals than in any other industry. The regulatory requirement for Quality Assurance (QA) in the pharmaceutical processing line takes the form of Validation (IQ OQ, PQ) of equipment and facility. Validation can run as high as 15 to 20% of the acquisition costs, and can take a year or more to complete for a novel system. The relative validation costs associated with the roller bottle processing alternatives are composite of both elements – equipment plus facility. The relatively simple equipment needed for manual processing requires minimal validation, while on the other hand, the complex automation in isolator option is a significant validation challenge. In contrast, the facility associated with the isolator options carries a relatively low validation cost, while the facility needed for manual aseptic processing carries a major validation cost. Combined, the validation costs for equipment plus facility is approximately the same for all three options at the pilot scale - *Table A, Line 5*. However, at the production scale, validation associated with the manual aseptic process is significantly more costly than that associated with the two isolator options, primarily resulting from the complex manual processing facility - *Table A, Line 14*.

Expanding the Economic Analysis – Labor Costs

There is no difference in labor costs between the options at the pilot scale as the minimum number of operators and technicians is required for all options - *Table A, Line 7*. At the

Pilot Scale (150 roller bottles per lot)				
Line	**Item**	**Manual**	**Glovebox**	**Automation in Barrier**
1	Equipment Capital Cost	$ 71,200	$ 446,200	$ 1,446,000
2	Total Acquisition Cost	$ 117,880	$ 671,200	$ 1,804,707
3	Infrastructure Capital Cost	$ 1,600,600	$ 698,450	$ 698,450
4	Utilities Capital Cost	$ 1,811,103	$ 711,433	$ 718,417
5	Validation Cost	$ 416,000	$ 224,000	$ 348,000
6	Environmental Control and Monitoring Annual Cost	$ 1,800,000	$ 720,000	$ 720,000
7	Labor Annual Cost	$ 181,440	$ 192,240	$ 168,734
8	System OEE[1]	10 %	15 %	3 %
9	**LIFE CYCLE COST**	**$ 26,188,107**	**$ 14,768,369**	**$ 14,993,859**
Production Scale (1500 roller bottles per lot)				
Line	**Item**	**Manual**	**Glovebox**	**Automation in Barrier**
10	Equipment Capital Cost	$ 252,000	$ 1,777,800	$ 1,976,200
11	Total Acquisition Cost	$ 353,640	$ 2,013,600	$ 2,378,100
12	Infrastructure Capital Cost	$ 3,166,550	$ 1,450,300	$ 1,091,750
13	Utilities Capital Cost	$ 3,730,654	$ 1,446,897	$ 1,130,228
14	Validation Cost	$ 803,000	$ 525,000	$ 489,098
15	Environmental Control and Monitoring Annual Cost	$ 2,140,000	$ 900,000	$ 800,000
16	Labor Annual Cost	$ 547,200	$ 551,520	$ 231,830
17	System OEE[1]	48 %	51 %	19 %
18	**LIFE CYCLE COST**	**$ 58,468,644**	**$ 41,905,967**	**$ 26,149,433**

[1] OEE = Overall Equipment Efficiency

Table A. Major LCC output data for a roller bottle at stream process. The economic impact of three different options for handling roller bottles at the pilot and production scale over a system life of 10 years is presented.

production scale, the economic advantages of automation with respect to labor costs are clearly seen. Even with considering assumed economies of scale, the manual options (both glovebox and open biohood) carry a labor cost that is more than twice that of the automated option (Table A, line 16), which is approximately the same as the cost at the pilot scale.

Apart from these direct costs, what other labor-related impacts do the options have? The impact of the options is immediately obvious from the appearance of the associated gowning requirements. However, apart from the costs of the gowns themselves, the costs associated with the different gowning requirements for Class B versus Class D are not easy to quantify. They include time and space for gowning and de-gowning; ease of movement within the gowns – and, hence, time requirements for carrying out manipulations and potential for human errors; allowable work periods and break requirements; intangible costs associated with general comfort level. These qualitative and intangible considerations can be assessed in a LCC model through assigning quasi-quantitative values that can be optimized over time through trending and experience. For example, qualitative or intangible considerations can be included in the LCC model by using a numerical ranking scale (e.g., 1-10), which is linked to quantitative inputs such as Out-Of-Spec (OOS) percentages or to Overall Equipment Efficiency (OEE). Primarily resulting from the savings in expensive highly skilled labor, in this example, automation in isolation is clearly the cheapest choice. When coupled with ergonomic and quality considerations, automation within isolators is the clear choice.

Expanding the Economic Analysis – Additional Considerations

Overall Equipment Efficiency (OEE) is the measure of the portion of time that the manufacturing equipment is actually processing material. OEE is equal to the equipment actual availability times performance times yield. Planned downtime is excluded from the measure of theoretical availability (also known as planned production time). Actual availability is impacted by such things as machine failure, small stops, start-up/warm-up, speed losses, set up and adjustments, and shut-down procedures. Change over between batches and between products can have a major impact on availability. Performance is measured as the cycle time (procedure time per unit) times the number of units processed, all divided by the planned production time. Yield is the number of units processed minus the number of units rejected, all divided by the number of units processed.

The pharmaceutical industry generally operates with low OEE. A typical pharmaceutical plant will operate somewhere around 30% efficiency.[11] Average overall equipment effectiveness is only 28% at the most inefficient companies, while the pharmaceutical industry-wide average OEE is less than 50%.[12] The industry's lowest OEEs are often found in biopharmaceutical processing facilities. There is room for significant improvement of OEE in the pharmaceutical industry.

In this case study, the poor system overall equipment efficiency for all three options at both pilot and production scale (Table A, Lines 8 and 17) is reflective of the significant process wait time in this example. This suggests that a sub-batch protocol, which represents the opportunity to capitalize on underutilized processing equipment, should be investigated. So, it can be seen that a robust LCC analysis can add decision making value in yet another way – it can provide process optimization indicators. In this case, the LCC analysis suggests that the process can be further optimized through a change in the process protocol. While potentially improving the efficiency of all three of the processing choices, it is apparent that a sub-batch protocol could utilize the automated system far more efficiently – increasing the potential output and further decreasing the total life cycle cost.

Some other inputs that should be considered in a LCC include maintenance costs, cleaning and consumables, and changeover and line clearance. These inputs are not significant in this example.

LCC: The Complete Economic Analysis – Putting it all Together

In spite of the high total acquisition cost (Table A, lines 2 and 11) and low OEE, the automation in barrier choice returns a LCC that is around half of that for the manual choice - *Table A, Lines 9 and 18*. This robust analysis reveals that the complex facility and attendant utilities costs, coupled with the ongoing high operating costs contribute to a surprisingly high LCC for the manual choice. The low OEE associated with the robotic arm in isolator system is indicative of an opportunity to optimize the process and even further lower the LCC.

Conclusion

LCC modeling can prove to be a valuable managerial decision support tool in sterile operations, particularly given the impending trend to increase automation. A rigorous and detailed LCC analysis can lead to counter-intuitive results, particularly when equipment acquisition and life cycle costs were compared. Specifically, at the pilot scale, the glovebox was the best economic choice, but that automation could become the desired economic choice if a higher value was placed on ergonomics.

Using a detailed LCC model, it was possible to demonstrate conclusively that an automated isolated solution was clearly the best choice at the production scale. Robotics within an isolator provided the best balance of overall cost, ergonomics, and product quality. A different choice might have been made if purchase price or purchase price and facilities costs alone had been considered.

In conclusion, life cycle cost modeling with LCC tools designed specifically for the pharmaceutical environment will become essential managerial decision support tools, particularly as discrete automation and the isolator-barrier field evolves. Indeed, by forcing the user to examine all aspects of the process from both financial and operating efficiencies, modeling of this type can be an important aspect

in the implementation of "risk based" GMPs. The value of LCC can be enhanced when used in conjunction with other modeling tools such as dynamic simulation when the latter is used to optimize process flows.

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Dr. Gomez discusses the goal of the Vaccine Research Center (VRC), significant changes in the development of vaccines to improve global human health, and possible new technologies that could challenge the drug manufacturing industry.

PHARMACEUTICAL ENGINEERING Interviews

Phillip L. Gomez, PhD, MBA, Director of Vaccine Production, Dale and Betty Bumpers Vaccine Research Center, National Institute of Allergy and Infectious Diseases

Phillip L. Gomez III is the Director of Vaccine Production at the Dale and Betty Bumpers Vaccine Research Center (VRC), part of the National Institute of Allergy and Infectious Diseases (NIAID). The NIAID is a component of the National Institutes of Health (NIH). At the VRC, Gomez is head of the Center's Vaccine Production Program. Gomez came to the Center from Baxter Healthcare Corporation, where he was senior director of process development in the vaccine business unit and project leader during the launch of the NeisVac-C™ vaccine in the United Kingdom. He was a project manager and director of product development at Aventis Pasteur. At Abbott Laboratories, Gomez held several positions in bioprocess development, including senior research scientist and team leader. He earned his Master's and Doctorate degrees, both in chemical engineering, from Lehigh University. He received an MBA from the Smith School of Business at the University of Maryland and a Bachelor's degree in engineering science from Dartmouth College.

Q How long have you been in your current position?

A I joined the Vaccine Research Center in 2001 as the first employee in the Vaccine Production Program.

Q What past experience best prepared you for your career with the VRC, and in particular, your current position as Director of Vaccine Production?

A I spent my previous time as Director of Process Development at Baxter Healthcare working on NeisVac-C™ scale-up and commercial launch (I was also corporate Team Leader for the commercial launch), Director of PD at Aventis (now Sanofi) Pasteur, and I started my career at Abbott Laboratories in BioProcess Development.

Q What do you like to do in your spare time, away from the office?

A My three year old daughter Zoë provides ample activities for all of my spare time as well as some of my non-spare time.

Q Could you give us some background on the VRC? How, why, and when was the VRC founded?

A Established in 1997 by former President Bill Clinton, the VRC is dedicated to improving global human health through the rigorous pursuit of effective vaccines for human diseases. The primary focus of VRC research is the development of a vaccine for HIV/AIDS.

The VRC building was completed in 2000 in Bethesda, Maryland, and Dr. Gary Nabel was

Inside the Vaccine Research Center

The Center's organization is similar to a conventional pharmaceutical industry drug development operation with laboratories engaged in basic discovery research, pre-clinical and clinical materials production, pre-clinical safety and efficacy testing, clinical research, and immunologic assessment of vaccine responses. VRC products have included candidate vaccines for AIDS, Ebola, Severe Acute Respiratory Syndrome (SARS), West Nile virus, and smallpox.

appointed as Director of the VRC in 1999. After September 11, 2001, the VRC expanded its role to include the development of vaccines against bioterrorism and emerging infectious diseases, while maintaining its primary focus on HIV/AIDS. Initially spearheaded by the NIAID, the National Cancer Institute, and the NIH Office of AIDS Research, the VRC is now an intramural division of NIAID. The VRC is named after Dale and Betty Bumpers, two long-time leaders in the causes of childhood vaccination and vaccine research. A former Governor of Arkansas and a US Senator, Dale Bumpers was the acknowledged leader on immunization issues throughout his 24-year career in Congress and was an advocate of funds to fight HIV/AIDS. Betty Bumpers is known for her joint efforts with Rosalynn Carter to improve the US immunization program. Their efforts led to the first US comprehensive childhood immunization initiative, which led to laws, now in every state, requiring certain vaccinations before entry into school.

Q What are your key priorities and responsibilities?

A My key priority is the Center's Vaccine Production Program, which is responsible for the manufacture, pre-clinical safety testing, and regulatory submission of VRC vaccines for clinical trials. The VPP develops processes and releases tests that provide material for up to Phase III clinical trials, with particular emphasis on techniques suitable for eventual large-scale manufacture of vaccines. The manufacture of candidate vaccines is outsourced to the biopharmaceutical industry, or takes place in-house in the VRC's new cGMP pilot plant.

Q How does your Agency interact with pharmaceutical and biotechnology firms?

A The goal of the VRC is to facilitate vaccine development by working with industry during product development. We have collaborations with large organizations such as Merck and Novartis as well as biotechnology companies such as Crucell, GenVec, and Vical.

The VRC's mission is to facilitate candidate vaccines that have tremendous technical challenges, and/or are not being developed by pharmaceutical companies (like an HIV vaccine), and "push" them down the product development pipeline until they can be picked up by industry collaborators for ultimate licensure and distribution.

Q Are you working with other regulatory agencies outside the US? Is there a collaborative process between EMEA and the FDA for example?

A NIAID/NIH has a tremendous number of programs (visit http://www.vrc.nih.gov/VRC/ for more information.) In the regulatory group at the VRC, we routinely interact with the FDA and international regulatory agencies, especially in the developing world, regarding vaccine development issues. The VRC has been involved in recent meetings on vaccine cell substrate regulatory issues as well as the potency evaluation of candidate HIV vaccines.

Q In addition to candidate vaccines for HIV, Ebola, SARS, and the West Nile Virus, is the VPP planning for a potential Avian Flu pandemic? How long would it take before an effective vaccine is produced?

A The VRC is doing research on the development of influenza vaccines and is currently manufacturing a candidate vaccine against a strain of avian flu. This vaccine will enter US Phase I clinical testing later this year. The VRC is examining ways to make a more broadly protective "universal influenza" vaccine, but this will take many years to develop.

Q Tell us about the Vaccine Pilot Plant. What cutting edge technologies, processes are designed into the manufacturing process?

A Central to the mission of the VRC is the ability to rapidly transition from basic research to clinical trials. Our new cGMP pilot plant is designed to help carry out this mission. Given the broad scope and mission of the VRC, the pilot plant was designed to manufacture a wide variety of vaccines. Currently, VRC candidate vaccines are based on genetic immunization strategies that utilize naked DNA (prokaryotic fermentation) and various viral vectors (eukaryotic cell culture). However, it was critical that the pilot plant was designed with sufficient flexibility to allow for the production of the widest technology base possible. The challenge of the design was to incorporate the maximum flexibility for a multi-product facility operating under the most stringent compliance environment. For diseases such as AIDS, for which the economic incentives may not be sufficient for industry to invest the resources necessary for advanced product development, the pilot plant was designed to allow for clinical production up to Phase III efficacy trials. Then, the technology is transferred to an organization that would seek licensure and distribution of the vaccine.

As a matter of fact, ISPE Baseline® Guides were used as a reference during the design of the pilot plant. In particular, the validation department used the ISPE Water and Steam Systems Baseline® Guide, Volume 4, and the ISPE Commissioning and Qualifica-

Vaccine Pilot Plant Facts and Figures

- Location: Frederick, Maryland
- Size: 126,900 square-feet
- Operated by Scientific Applications International Corporation – Frederick, Inc. (SAIC-F) as part of the National Cancer Institute Federally Funded Research and Development Center in Frederick, Maryland
- Contains four independent production trains, with two trains operating at 100 Liter scale, one train operating at 400 Liter scale, and one train operating at 2,000 Liter scale
- Contains a central inoculum preparation suite
- Contains a media/buffer preparation suite which provides for internal manufacture of all solutions for the operation
- Fill suite is easily accessible from the production trains and have the capability of performing smaller scale lots up to 5,000 units and larger scale work up to 30,000 units
- Warehouse is sized to handle raw materials and supplies sufficient to maintain all four production trains operating simultaneously with coordination and control through the adjacent dispensary
- Quality control laboratories are designed to provide all necessary testing activities including raw materials, environmental monitoring, bioburden, water for injection and pure steam analysis, bulk and final product sterility, and in-process and final product release
- A quality assurance department is responsible for oversight of cGMP manufacture including validation, compliance, lot release, and document control

tion Baseline® Guide, Volume 5, as a reference for developing and commissioning the I/OQ documents.

Q What significant changes do you anticipate in the next few years?

A There are many new technologies that are attempting to impact the manufacture, aseptic filling, and distribution of influenza vaccine. Multiple cell-based methodologies for producing influenza vaccines are under development which will try to displace the current egg-based methods. Even with the success of these technologies, the ability to manufacture hundreds of millions of doses of influenza vaccine will greatly challenge the engineering systems used for aseptic filling, cold-chain, and product distribution channels.

Q What technological and operational breakthroughs do you anticipate within the next five years?

A In the next five years a new group of technologies for vaccines will be evaluated to see if they will become the next generation of vaccines. Historically, vaccines have been slow to adopt new technologies (recombinant DNA techniques, delivery methodologies, adjuvants), but a tremendous number of new vaccines, if successful, may change this. Technologies such as DNA plasmids, adenoviral vectors, and novel adjuvants are all under extensive evaluation for diseases like HIV, malaria, and tuberculosis.

Q Is there anything else that you might want to say to our readers? Any last thoughts?

A Vaccines have traditionally been produced in relatively small-scale, dedicated facilities located at a few companies, but the challenges of emerging infectious disease, re-emerging infectious diseases, biodefense, and HIV may result in novel technologies for production as well as a group of new entrants into the vaccine fields, which should provide new and exciting challenges for the engineers who provide the infrastructure to manufacture them.

Gomez photo courtesy of NIAID.

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Comparison of Campaign vs. Concurrent Large-Scale Cell Culture Facilities

by Dr. David Estapé and Frank Wilde

This article compares a campaign with a concurrent large-scale cell culture manufacturing facility; including advantages, disadvantages, investment cost, and production capacity.

Introduction

The biopharmaceutical market has a significant growth rate strongly driven by the production of monoclonal antibodies. Consequently, in recent years, the number of large-scale cell culture facilities has experienced a significant growth that is expected to continue.[1]

Biopharmaceutical companies are looking to build efficient production plants to best fit their demands. At first, low investment and short realization time are the main interest. However, in the long term, a well established production plant model will be equally or even more important.

Multi-product production facilities have become almost a "must have" when approaching the realization of a new plant. In some cases, the plant is envisaged as a mono-product facility. Even in these cases, certain multi-product design features are included.

There are two basic organization types of a multi-product facility: the Campaign Production Facility (CampPF) and the Concurrent Production Facility (ConcPF). In the CampPF, different products are produced in different time periods, or campaigns, separated by a changeover phase. In the ConcPF, two or more products are produced at the same time at different production areas or suites. In each individual suite, it is also possible to manufacture different products on a campaign basis.

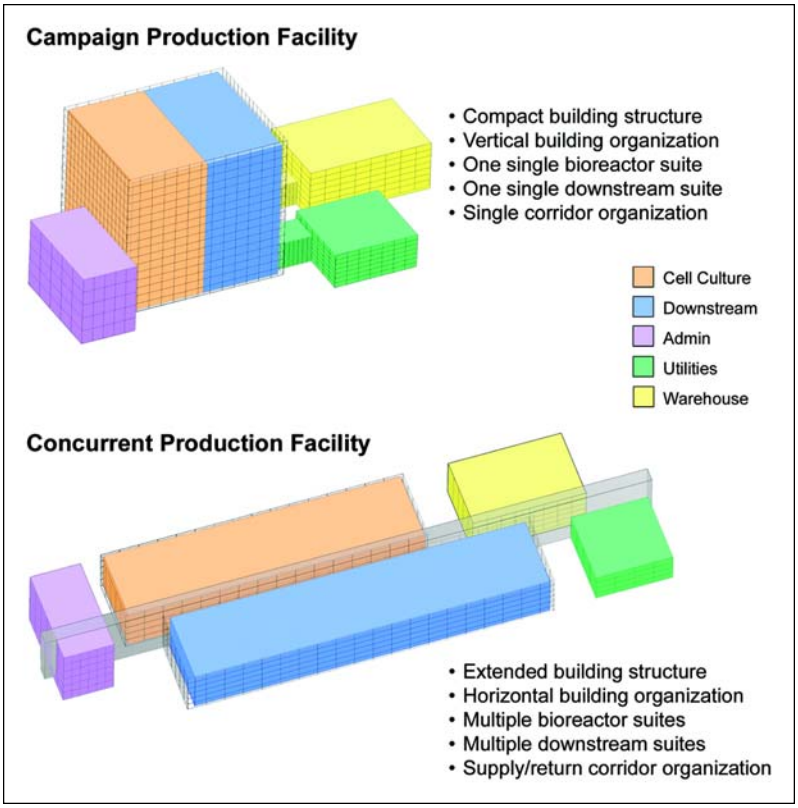

Figure 1. Main building organization characteristics of campaign and concurrent large-scale cell culture facilities.

From the GMP point of view, both types of organization represent different approaches to minimize or avoid potential cross-contamination between products, a main compliance concern.

In the design of a new production facility, the first approach may favor the ConcPF due to higher flexibility. This is based on the capability to produce two or more products simul-

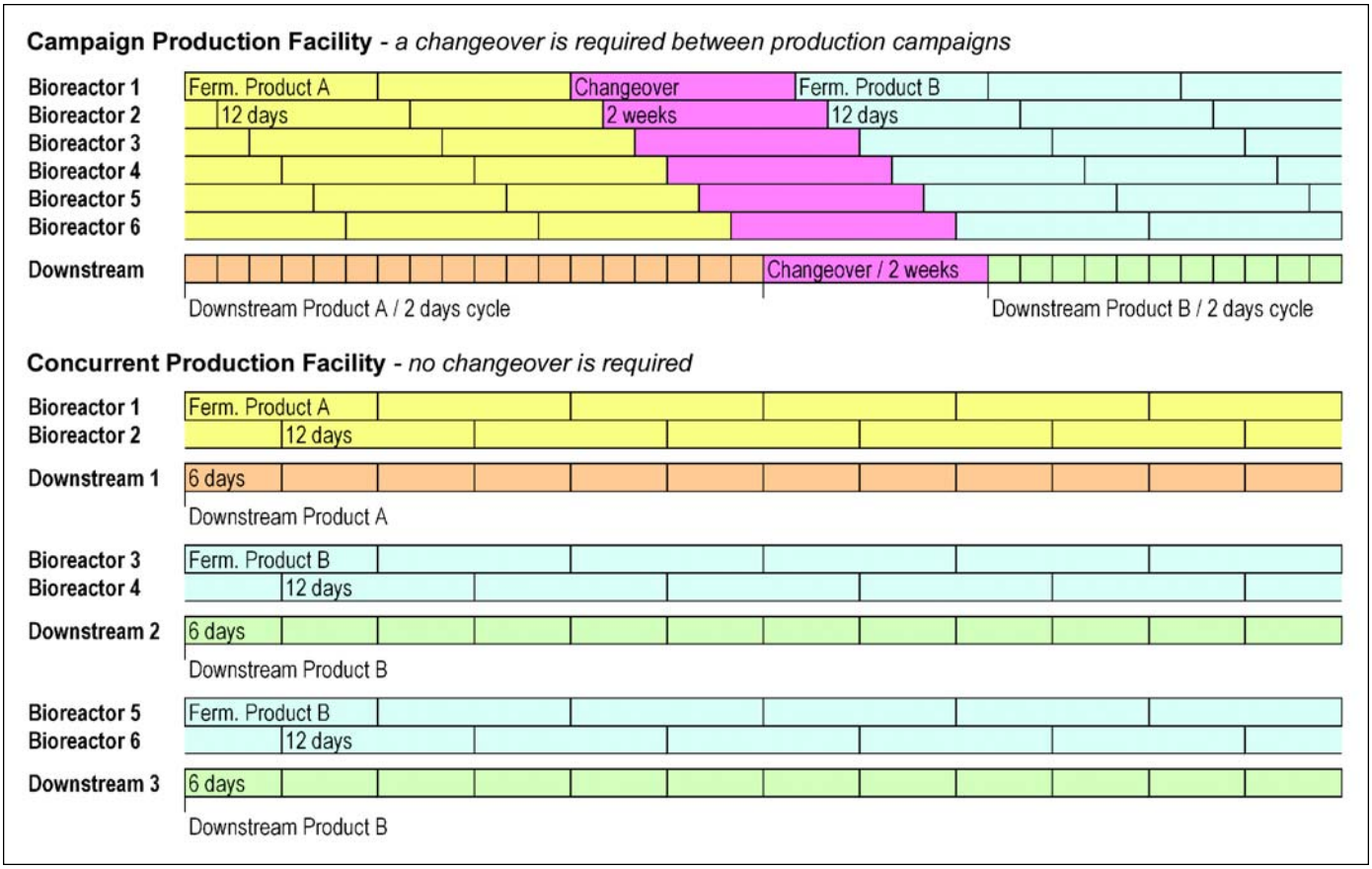

Figure 2. Production schedule of campaign and concurrent large-scale cell culture facilities.

taneously. However, one also can expect higher investment costs based on a large number of equipment needed if two or more products are manufactured in parallel.

The final decision to plan a CampPF or a ConcPF may require determining how much flexibility is needed and the related costs. High flexibility and low investment costs would be ideal, but seem to be contradictory.

In reality, both facilities are organized totally different and also will have different requirements. The result is two designs that are not easy to compare and more difficult to qualitatively identify advantages and disadvantages for an objective evaluation. Finally, only an extensive analysis can help to identify the appropriate design for a specific business case.

This article compares a CampPF with a ConcPF for large-scale cell culture manufacturing. It looks into the facility organization, process design, as well as investment costs and production capacity. The goal is to quantify and define how much more costly and how much more flexible a ConcPF is compared to an equivalent CampPF.

Case Study

A biopharmaceutical company is planning to build a new large cell culture production facility. The facility should be equipped with six main production bioreactors with 10,000 liters working volume each. If we assume 12 days cultivation cycle, an average titer of 1.2 g/l, and an overall yield of 75%, the anticipated theoretical total maximum annual production capacity is up to 1,600 kg of protein.

Facility Organization

The facility will be located on an existing production site. The site will provide basic infrastructure like general utilities (i.e., black steam, etc). Apart from the production core, the plant will include three additional modules: a production administration building, including QA/QC, a Just-In-Time (JIT) warehouse, and a central utility area for generation and distribution of process utilities (i.e., process water, etc).

Both facilities will be organized following state of the art design principles[2] that will secure a good GMP level. The production core will be divided between upstream and downstream areas. Furthermore, the upstream area will be organized in different production disciplines like media preparation, inoculum preparation, and harvest apart from the bioreactor suite(s). The downstream area will be divided in buffer preparation, buffer holding, and pre-viral and post-viral removal downstream suites. Other support areas like product storage, washing areas, etc., also will be integrated.

The main difference between the CampPF and the ConcPF will be the number of bioreactor and downstream (pre and post-viral) suites. The CampPF will have only one single bioreactor suite, one pre-viral, and one post-viral removal downstream suite. On the other hand, the ConcPF will have three suites of each type to be able to produce three different products simultaneously and independently from each other.

Apart from the number of suites, the design of each facility will follow opposite design strategies. Whereas the CampPF will be a high and compact building, the ConcPF will be low

and broad. The design strategy could be different, but the intrinsic characteristics of each facility support the preferred designs. In the CampPF all equipment will be dedicated to one single product. This allows a higher integration or optimization that will lead to the compact design. In the ConcPF, there will be a core facility that is repeated as many times as the number of products that can be manufactured simultaneously. This repetition will lead to the wide horizontal design.

Figure 1 summarizes the main characteristic of each plant and shows the main building structure as it is described below.

Campaign Production Facility

The facility will be organized around a compact production building. The administration-QA/QC module, the JIT warehouse, and the utility module will be attached to facilitate a good personal and material flows, in addition to a well organized utility distribution. The production building will be internally divided between upstream and downstream and will have a vertical organization to facilitate process gravity flow. So, media preparation as well as the seed train is envisaged to be located in an upper level above the bioreactor suite. Similarly, buffer preparation will be located above buffer holding that will in turn be above the downstream suites. The different production areas in the fermentation or in the downstream will be arranged around a single corridor.

Concurrent Production Facility

The facility will be organized in different modules around a central corridor or spine. In that case, upstream will be a totally independent module from downstream. Both modules will be organized horizontally, limiting the gravity flow. The three different bioreactor suites or the three downstream suites will be located one next to the other and linked to a supply and a return corridor to facilitate unidirectional flows.

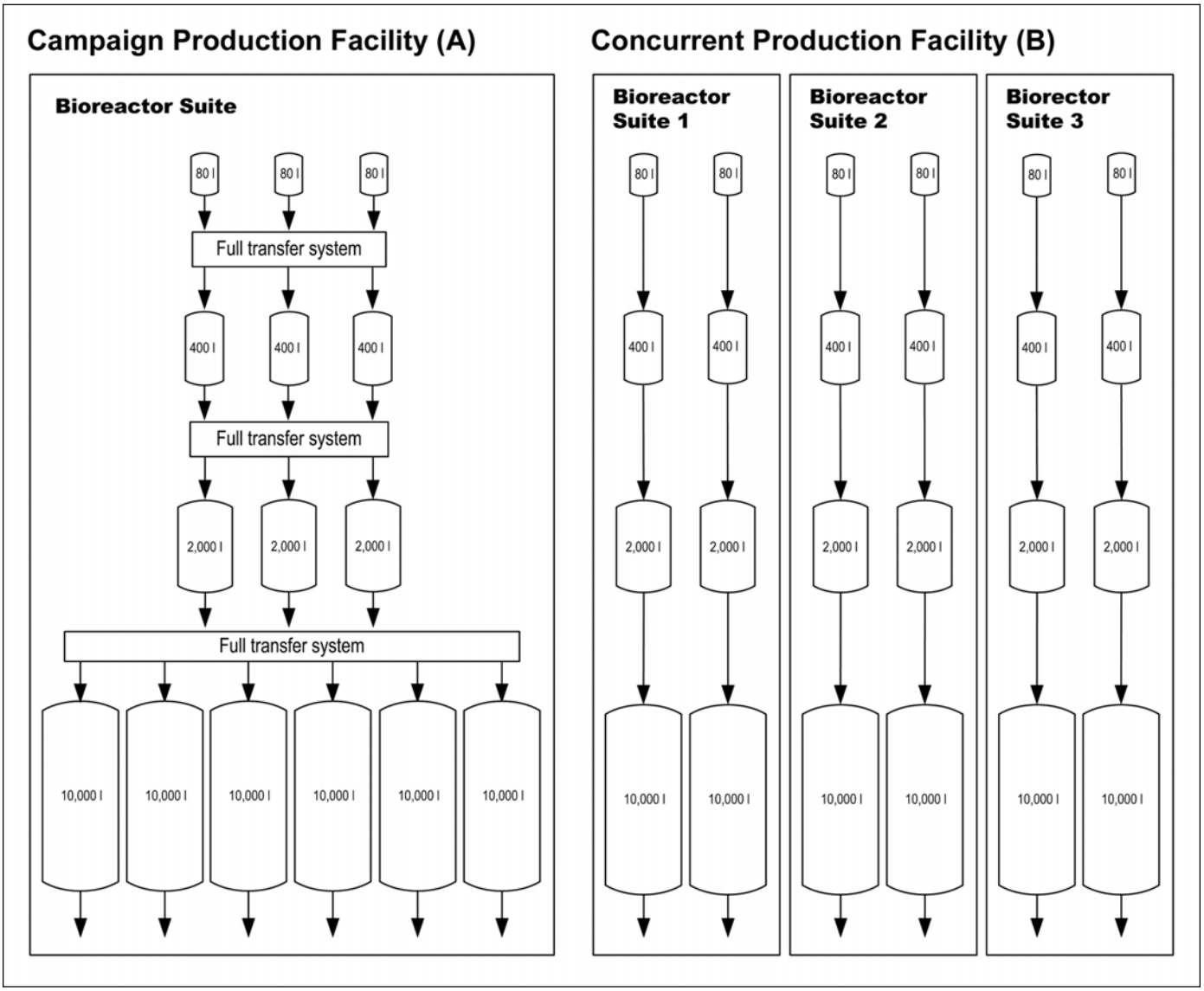

Figure 3. Upstream design of a campaign large-scale cell culture facility (A) and upstream design of a concurrent large-scale cell culture facility (B).

Process Design

Cultivation times are longer than downstream processing times and are the limiting step. This allows two or more bioreactors to share a common downstream suite. The number of bioreactors per downstream suite is defined by the relation of the cultivation and the downstream processing times. The production cycle time is then defined by the cultivation time divided by the number of bioreactors.

In the CampPF, all six bioreactors will share a single downstream suite. Assuming a cultivation time of 12 days, one batch will be transferred to downstream every two days. A two day cycle time is closed to a typical net downstream processing time. The net downstream processing time is only the intrinsic time required to carry out the process and does not include time for cleaning and sanitization. Consequently, the equipment that has been already in use is cleaned and sanitized at the same time processing continues uninterrupted. In addition, the downstream suite or each production step must be "fully equipped." In a "fully equipped" suite, there is enough equipment that processing does not need to be interrupted by waiting for a piece of equipment to be available.

The maximum theoretical number of pieces of equipment in the CamPF can be reduced by maximizing the equipment utilization time or in other words, minimizing the equipment not in use. However, this equipment optimization can not compromise processing and equipment is always available at the time it is needed to continue production without interruption.

This equipment optimization is possible if the same equipment is used simultaneously or at a different time for different production steps. In that case, the shared equipment has multiple connections to the different users (i.e., production steps). The high number of possible transfers or connections represents a higher plant complexity (i.e., multiple piping, large number of valves, higher automation effort, etc).

In the ConcPF, two main 10,000 liter production bioreactors will be installed in each of the three bioreactor suites. Two bioreactors will share one downstream suite. If we assume again a 12 day cultivation time, one batch will be

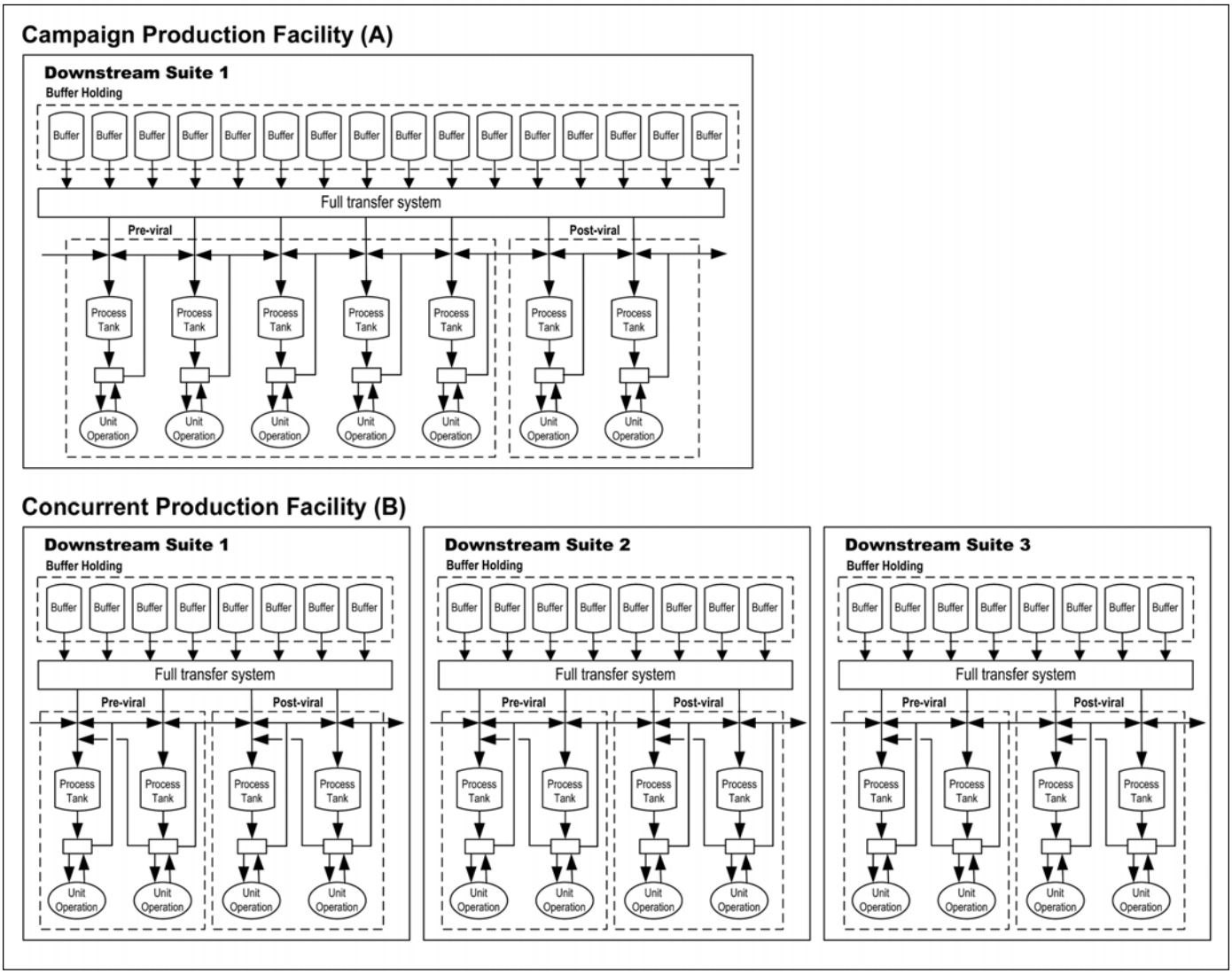

Figure 4. Downstream design of a campaign large-scale cell culture facility (A) and downstream design of concurrent large-scale cell culture facility (B).

transferred to downstream every six days. If the net downstream processing time is again limited to two days, there will be sufficient production time left, four days, that cleaning, sanitization, and processing do not need to be performed at the same time.

In that case, it is possible to further simplify the number of pieces of equipment by an extended reuse of the equipment during production. So, the equipment used in an earlier step can be cleaned and sanitized and then used again in a later step. In that case, processing may need to wait until the equipment is available again.

Figure 2 shows an example of a time line for the production of two products for both facilities. In the CampPF, an upstream batch is transferred to the downstream every two days. In the ConcPF, the transfer occurs every six days in each suite. In this case, three upstream batches from the three bioreactor suites are transferred simultaneously, each batch to one of the three different downstream suites. In other words, the maximum downstream processing cycle is limited to two days for the CampPF and six days for the ConcPF. The longer downstream cycle of the ConcPF is required due to the reuse of equipment and includes the time for cleaning and sanitization between consecutive process steps. The short downstream cycle of the CampPF requires a higher processing efficiency. Cleaning and sanitization occur simultaneously to processing, thus, resulting in a shorter cycle.

Bioreactor Suite Process Design

Figure 3A shows the design of the bioreactor suite for the CampPF and can be directly compared to the envisaged design for the ConcPF shown in Figure 3B. The differences are discussed below.

For the ConcPF, two main 10,000 liter bioreactors will be installed in a single suite. Each production bioreactor will have a dedicated seed train. As a result, there will be eight bioreactors of different volumes per suite. The three suites together will then hold a total of 24 bioreactors. Each bioreactor can only transfer to one single bioreactor (except the production bioreactors that will transfer to downstream). There are only 18 possible transfers between bioreactors.

For the CampPF, the six main 10,000 liter bioreactors will be installed in the single cultivation suite. All will share an optimized seed train with only three seed bioreactors for each seed culture group. The total number of bioreactors in the CampPF will be 15 units, 38% less than in the ConcPF. The reduction of the number of the bioreactors is possible by optimizing the utilization time of each group of seed bioreactors since the seed cultivation process is usually shorter than the main production cultivation.

However, there will be multiple transfers possible between a seed bioreactor and the next consecutive bioreactor group. As a result, the total number of transfers in the CampPF will increase to 36, 100% higher than in the ConcPF design. This results in a higher plant complexity (i.e., multiple piping, large number of valves, higher automation effort, etc).

Downstream Suite Process Design

Figure 4A shows the design of the downstream suite for the CampPF. It can be directly compared to the envisaged design for the ConcPF shown in Figure 4B. The differences are discussed below.

In the CampPF, the downstream suite will consist of seven processing stations. Each station will include a product tank and a docking location where different types of unit operations can be connected. The station will be piped to allow recirculation (i.e., from an ultra-filtration unit) or transfer to the next station (i.e., after a chromatography step). So, the product will move from station one to seven as long as the successive purification steps take place. The first five stations will be dedicated to pre-viral purification steps. The last two stations will accommodate the final purification steps after post-viral removal. All stations will share a common buffer holding group consisting of 16 tanks of different volumes. The number of buffer tanks can be optimized to the number of buffers used (each buffer tank should be dedicated to a single buffer). The buffer distribution system will allow a transfer from each buffer tank to each station.

During a product campaign, all necessary unit operations should be connected in the sequential order to the downstream stations. In this arrangement, the different purification steps are carried out in sequence without interruption. Cleaning and if necessary sanitization steps occur parallel to the purification steps. The unit operations will only be interchanged between product campaigns.

Summarizing, there are seven different product tanks/stations and 16 buffer tanks, a total of 23 tanks. The buffer distribution will allow 112 different buffer transfers.

In the ConcPF, each of the three downstream suites will consist of four stations, two for pre-viral and two for post-viral processing. The design of the station will be similar to the CampPF, but it will be possible to transfer the product back to a previous station. An exception will be between pre- and post-viral steps. So, the product may be moved forth and back between stations in order to reuse stations. By reusing stations, it is not possible to clean or sanitize the equipment parallel to the purification step. The design also should facilitate interchanging the unit operation connected to the station during processing of one batch.

Each downstream suite will have a buffer holding group of eight tanks of different volumes. Each tank will be used for holding different buffers during the purification process. In addition, to ensure a higher flexibility, the buffer distribution system will allow a transfer from the eight buffer tanks to the four stations.

Summarizing, there are 12 different product tanks and 24 buffer tanks, a total of 36 tanks overall or 12 tanks per downstream suite. The buffer distribution will allow 32 different transfers per suite or a total of 96 transfers for the three suites. This represents a 57% increase on the number of tanks and a 14% decrease on the number of buffer transfers in respect to the CampPF.

Similarly, a defined number of media preparation, buffer preparation, harvest tanks, and the required transfers or connections are analyzed.

		Campaign	Concurrent
Main Equipment	Tanks	54	75
Main Transfers	Transfers	360	320
Automation	I/O	14,500	16,300
Piping	km	40	70
Manufacturing Building			
Volume	m^3	75,000	120,000
Area	m^2	17,800	29,600
Total Investment Cost	M€	225	320
	M$	282	400

Table A. Key design figures of a large-scale campaign and a concurrent cell culture facility.

Major Key Figures and Cost

The major typical key figures that define the facilities as described above are summarized - *Table A*.

The Table shows that the ConcPF will require a large number of pieces of equipment, but will not be as complex as the CampPF as a result of the number of transfers. There will be approximately seven transfers in average per main equipment in the CampPF, whereas there will only be four in the ConcPF.

The large number of pieces of equipment together with the organization of the building around a central spine/corridor and the production modules structured between supply and return corridors will make the ConcPF significantly larger in size than the CampPF.

From key figures and based on facility benchmarks we are able to estimate the corresponding total investment cost for each facility. The projection for the CampPF is €225 million ($282 million), whereas the projection for the ConcPF is estimated to €320 million ($400 million), which is 42% higher.

Concluding, the ConcPF will require a large investment based on a large number of pieces of equipment and building size. However, the cost of the ConcPF will not be as high as if it is assumed to be directly proportional to the cost of the CampPF because of its lower complexity.

The higher cost of the ConcPF seems to be a major disadvantage. However, the study would not be complete if it is limited only to the investment cost. As already mentioned, we would expect a higher flexibility for the ConcPF. In that case, it is important to analyze the production capacities for each facility.

Production Capacities

If the facilities are dedicated to one single product per year, they can be regarded as mono-product facilities. In that case, all six production bioreactors of each facility are manufacturing the same product the entire year without interruption other than maintenance. If the cultivation step is the process bottleneck, both the CampPF and the ConcPF will be able to produce the same amount of product at the end of the year. This amount of product defines the maximum capacity (or 100%). It corresponds to 1,600 kg/year based on the assumptions already described.

The production capacity will differ when two or more products are manufactured. The production of multiple products requires a changeover period between product campaigns. The changeover is regarded as a downtime or a loss of production capacity. The changeover phase in the CampPF will affect the entire facility since it will affect both, the single bioreactor suite and the single downstream suite. On the other hand, the changeover in the ConcPF may not necessarily affect the entire facility and may be limited to one or two suite groups (one bioreactor suite and one downstream suite). It can even be that the changeover phase is not required at all. As a result, the decrease of production capacity due to changeover downtime will be higher for the CampPF than for the ConcPF.

Figure 2 also shows the changeover phase between two product campaigns, product campaign A and product campaign B. If the product demands require dedicating two thirds of the annual production capacity to product A and one third to product B, only one changeover is required in the CampPF, but no changeover will be necessary in the ConcPF. In that case, two suite groups will be dedicated to product A and one to product B. The total production capacity of the ConcPF will be higher based on longer production time of two weeks.

The total downtime or capacity drop will depend on the number and the length of the changeovers. For the ConcPF, it also will depend on the number of suite groups affected by the changeover.

First, the number of changeovers depends, at the end, on the number of products to be produced. For more products, more changeovers are required and the loss of production capacity is more significant.

Second, the length of the changeover time depends on a large number of factors, including the complexity as well as the organization. That makes it difficult to define and should be based on actual data. In any case, a special effort should be made to minimize the required time.[3]

For example purposes, a two week period has been defined

Product/Year	Campaign	Concurrent
1	100	100
2	96	99 - 100
3	91	97 - 100
4	87	96 - 99
5	83	94 - 97
6	79	93 - 96
7	74	92 - 94
8	70	90 - 93
9	66	89 - 92
10	61	87 - 90

Table B. Production capacity for a large-scale campaign and a concurrent cell culture facility depending on the number of different products to be manufactured per year. Production capacity is given as a % of the maximum capacity that corresponds to the mono-product facility (one product). Production downtimes were calculated based on a two-week changeover period.

and seems to be a reasonable and feasible changeover time for a large cell culture facility. The same changeover time has been used for the CampPF as well for the ConcPF. It could be argued that the smaller suites in the CampPF may require a shorter changeover time. Note also that a changeover shorter than 12 days (i.e., one week) will mean that two different products will be produced simultaneously in the bioreactor suite of the CampPF. Simultaneous production of different products in the same production suite may be regarded as a risk for cross-contamination or potential errors since two completely different production campaigns have to be followed simultaneously.

Finally, the number of suite groups involved in the changeover in the ConcPF will depend on the demand or in the distribution of the production capacity assigned to each product. This may be different each year and depends on real scenarios. Nevertheless, the drop of production capacity can be defined within a range determined by the minimum and maximum number of suite groups involved in product changeovers.

Table B summarizes the expected loss of production capacity as a function of the number of products for a two week changeover period for the different types of facilities. It is important to note the higher production capacities of the ConcPF compared to the CampPF. For example, with six products per year the production capacity of the ConcPF is 19% higher than the CampPF.

The loss of production capacity is the major drawback of the CampPF and shows the flexibility of the ConcPF. It is clear that the number of products per year should be limited in a CampPF.

Cost of Goods

The combination of the total investment cost and the production capacity should be the key to define the advantages or disadvantages of the CampPF and the ConcPF. An approach could be through the calculation of the Cost Of Goods (COG) where both variables are combined.

The calculation of COG is defined by a large number of variables that, depending on how they are identified, may introduce a large uncertainty on the final conclusions. A qualitative discussion on the COG for the CampPF and the ConcPF is presented below.

The COG is determined by the sum of all cost incurred in the manufacturing of a product, divided by the total amount of product manufactured. Included in the overall manufacturing cost is the depreciation or capital cost that depends on the total investment. The total output of the facility is determined by the capacity.

The depreciation is the investment cost divided by the total amortization time. Different companies use different amortization times of 10, 15, or even 20 years. It also can be that different amortization times are applied to different concepts (i.e., building, equipment, automation, etc). What is important to note is that the investment cost is diluted by the amortization time and will have a lower impact on the COG than it could initially be expected. In addition, the depreciation is added to all other manufacturing costs that can be as high as or even higher than the depreciation. This dilutes even more the influence of the investment cost in the COG. At the end, depreciation cost may account for 30% to 40% of the COG. [4,5]

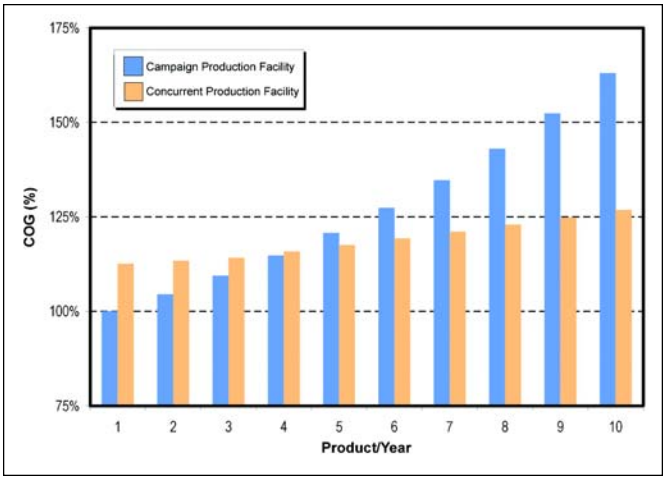

Figure 5. COG of campaign and concurrent large-scale cell culture facilities depending on the number of products to be manufactured per year. COG is given as a % of the minimum COG that corresponds to the campaign facility when only one product is manufactured. The calculation assumes a decrease of production capacity with the increase of the number of products as depicted in Table B. Depreciation was proportional to the total investment costs as described in Table A. All other costs were considered constant.

On the other hand, the production capacity has a direct influence on the COG through the total amount of product manufactured. It is shown that a decrease in the capacity utilization from 100% to 80% may represent an increase of the COG sold from $300/g (240 €/g) to $375/g (300 €/g), a 25% increase.[1]

Therefore, the higher investment cost of the ConcPF is diluted and may no longer be the main economical factor. In contrast, the expected lower capacity of the CampPF affects directly the COG that will significantly increase.

The key factor that defines the cost efficiency of the CampPF or the ConcPF is the number of products manufactured in the facility each year - *Figure 5*. As more products are manufactured, more production downtime for changeover occurs. The production capacity is then lower and consequently the COG increases. The increase of the COG is much more severe for the CampPF since the capacity is much more sensitive to the number of products manufactured.

When a limited number of products is manufactured, the loss of production capacity of the CampPF is limited. Consequently, the COG of the ConcPF will be higher due to the higher investment. The extreme example will be when only one product is manufactured. Both facilities can produce the same amount of product, but the ConcPF will require a higher investment. The COG of the ConcPF will be clearly higher than for the ConcPF.

When the number of products is high (eight to 10) there is a significant decrease of the production capacity of the CampPF compared to the ConcPF. It can happen that the COG of the ConcPF is more attractive than for CampPF due to its higher production capacity.

In other words, the higher investment cost of the ConcPF

is easily compensated by the higher capacity for multiple products per year. At the end, the COG for both facilities may not differ in a great extent.

Even if the COG of the ConcPF is higher than that corresponding to the CampPF, the ConcPF may be still the choice. In that case, the higher production capacity can provide more product to the market and combined with the earnings margin of high value products may easily pay for the higher investment.

Conclusion

The capital investment of a biopharmaceutical company on a new multi-product production facility is an important business step that needs to be well evaluated. The selection of the correct type of facility is an important piece of this study. The CampPF or the ConcPF are the two facility models of choice. Each has different advantages and disadvantages in the short as well as in the long run.

The CampPF allows an important optimization of the number of pieces of equipment, but requires a complex transfer strategy between equipment. The result is a compact, but complex facility with a lower initial capital investment. In the CampPF, the changeover between two product campaigns represents an important loss of production capacity since the complete facility is affected.

The ConcPF requires a large number of pieces of equipment to be able to manufacture different products simultaneously, but with a simple transfer strategy. The result is a large facility that will require a larger initial investment. The production capacity in the ConcPF will be much less affected by the changeover between product campaigns. On one hand, different manufacturing campaigns can be easily distributed in different production areas of the facility; on the other hand, only part of the facility is affected during the changeover period.

When only few products are envisaged to be produced in a multi-product production facility, the CampPF model is the best choice. It will provide the required multi-product capabilities at the lowest investment cost and guarantee the most economical COG. However, when a high number of products need to be manufactured each year, a CampPF can become unproductive. In that case, a ConcPF would allow a better allocation of the multiple campaigns and still guarantee a high production capacity. The initial higher COG due to a higher investment volume becomes more cost-effective.

Nonetheless, the critical number of products at which a CampPF facility is no longer attractive depends on a large number of variables (investment cost, changeover time, manufacturing cost, etc) that need to be determined case by case. The final selection between both types of facilities also should not be an isolated analysis depending only on the intrinsic characteristics of each facility. The different advantages and disadvantages have to be looked at taking into account all external and strategic factors case by case.

For example, if a biopharmaceutical company needs to invest for their first large-scale multi-product production facility, it may be an advantage to invest in a ConcPF with its higher flexibility (if a high flexibility is needed and the investment cost is not a limitation). However, if the biopharmaceutical company is already well established and has one or more existing facilities, it may prefer a CampPF with a lower investment since the flexibility may be secured by combining all production plants.

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Wireless Framework for Enterprise Excellence: Managing, Securing, and Validating

by Janice Abel, Hesh Kagan, and Ian McPherson

This article describes management strategies to overcome uncertainty, cost, and regulatory vulnerability in wireless implementations.

The radio spectrum is an asset that pharmaceutical and biotechnology industries are now beginning to exploit, and the emergence of secure, affordable wireless technology is making it easier for them to do that every day.

Wireless technologies include wireless access points (gateways), transmitters, receivers, antenna, protocols, powering options and servers, and security technology ranging from intrusion detection devices to data encryption. Performance and reliability of wireless technology has been improving steadily, to the point at which it has become a very feasible cost saving option for many industrial applications. Unlike cell phone networks which span many miles, most industrial settings are contained, repeatable, and thus very manageable, provided that the system is implemented at the enterprise level.

The most significant challenges to pharmaceutical companies wishing to take advantage of wireless technology are in managing the limited available bandwidth, integrating multiple communication protocols and standards, and maintaining and supporting the ongoing security requirements of wireless networks. Solving these problems requires resource planning, performance management, and a common wireless systems management platform.

This finite, relatively available resource means that today - and for many years to come - reaping the many control benefits of wireless communications will challenge technology management much more so than technology performance.

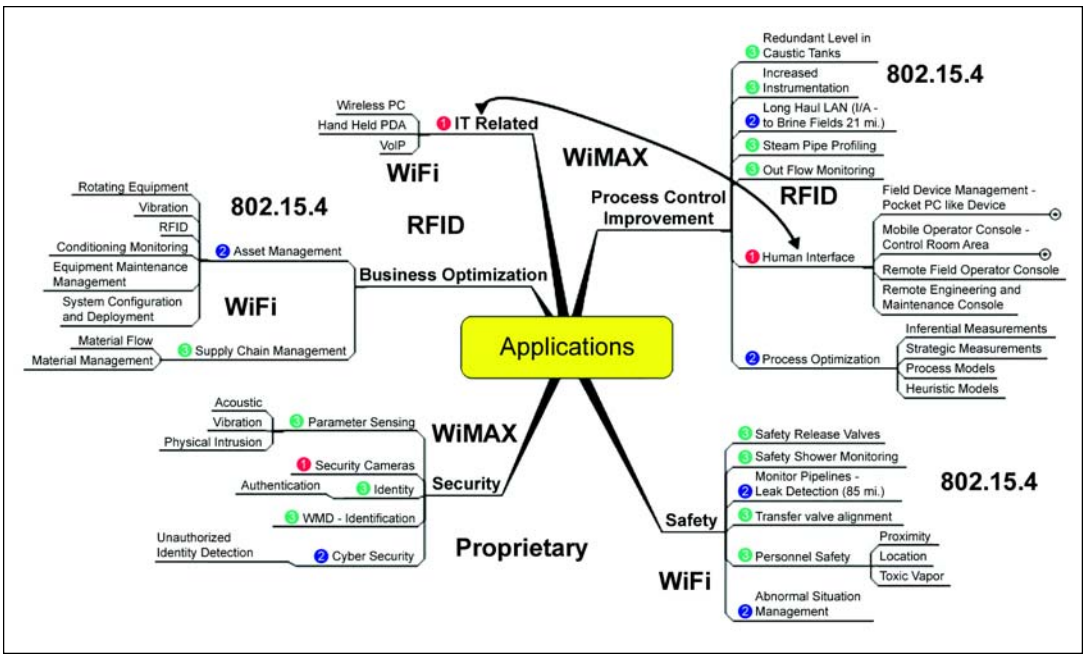

Figure 1.Typical interrelated applications with different RF "needs."

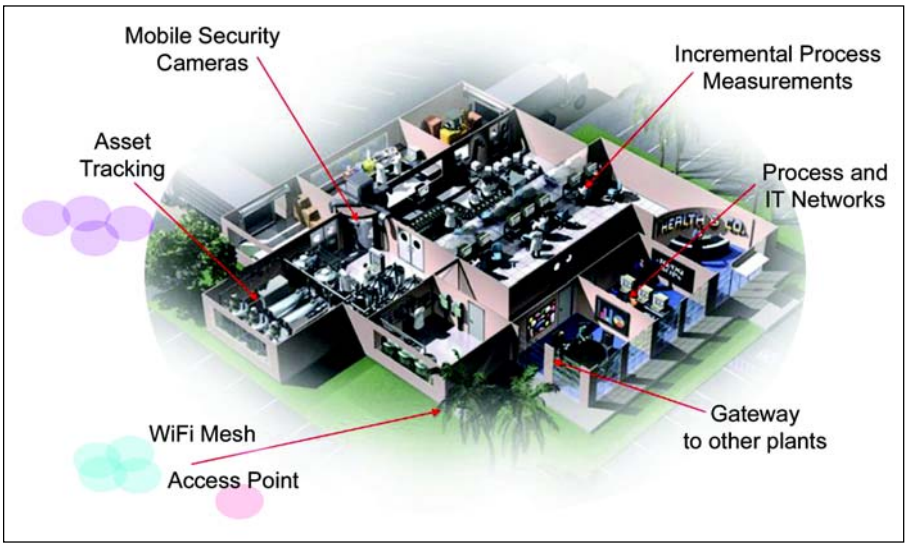

Figure 2. Potential wireless application areas for pharmaceutical facilities.

Figure 1 illustrates the broad range of manufacturing areas that are now implementing some type of a wireless solution. For years, the medical device industry has been using wireless technology in such applications as intravenous pumps, pacemakers, wheelchairs, and more recently for metering insulin injections via a patch that calculates sugar intake and sends a wireless signal to the patch for dosing, with very good results. In September 2000, the Center for Device and Regulatory Health (CDRH) issued a guidance for industry, entitled Wireless Telemetry Risks and Recommendations.

As a result, the FDA has been examining the use of telemetry and ElectroMagnetic Interference (EMI) in medical devices – especially since the FCC opened up radio frequency usage in December 2005 for a previously restricted medical device radio spectrum and has advised switching frequencies on some devices to avoid interference. More applications are just beginning to emerge in this industry.

"Pharmaceutical industry, business systems, such as Enterprise Resource Planning (ERP) software, which seeks to integrate financial and operations data company-wide, have been successfully using wireless technologies in the pharmaceutical industry for many years. The functional scope and range of these applications for the most part has been isolated to providing control flexibility and validation for discrete processes," said Mike Howden an Invensys Validation Technologies consultant, adding that Invensys has developed new programs to train technical staff in expanding validated wireless applications in pharmaceuticals. Other common wireless applications manage personnel access for security purposes.

If wireless proliferates in the pharmaceutical industry as it has in other industries, those who purchase and implement point solutions will likely enjoy some initial success. But as use spreads to different departments and different locations, the joys of wireless freedom will likely begin to fade. Users may begin experiencing increased interference on the links. Transmission may be interrupted. There may be availability problems, data loss, and performance degradation. Furthermore, this ad hoc approach fails to consider the varying criticality and time sensitive aspects of disparate application data that are contending for use of the spectrum. If this growth continues unmanaged, the technology that would potentially offer a method to improve productivity, efficiency, and cut costs, also could add uncertainty, cost, and regulatory vulnerability.

The Need for Systems Management

Fundamentally, wireless networks deliver the same basic business benefits as wired networks: they connect data point A to data point B, enabling timely information sharing for a wide range of application and reporting functions. But because of the low cost of wireless sensors, and the no-cost of running wires, more points can be connected far more cost-effectively than wired networks. Wireless networks enable detailed measure of process variables, including measures of quality which could not be measured at all before, for example, increasing process performance in applications which previously required mandatory laboratory analysis. Freed from the restrictions of wires, it is possible to set up measures for virtually any point of the enterprise and receive this information in real time.

Because of the finite amount of radio spectra at its disposal, care must be taken upfront to determine where the technology will be most beneficial. Figure 2 shows some of the areas in which wireless technology could benefit pharmaceutical and other bioscience manufacturers. Following are more examples of benefits that wireless implementations could deliver the pharmaceutical enterprise:

Enterprise Management

- real-time monitoring of parts and finished goods, across the entire value chain
- tighter process monitoring by increasing the number of checkpoints across the enterprise or in remote locations (e.g., cold chain application)

Logistics

- Radio Frequency Identification (RFID) for supply chain to prevent counterfeiting of drugs or improve product tracking and security
- improved management of shipping receipts and returns processing
- improved inventory management, forecasting, and planning

Safety and Security

- managing plant and system personnel access

Production

- improved process execution by en-

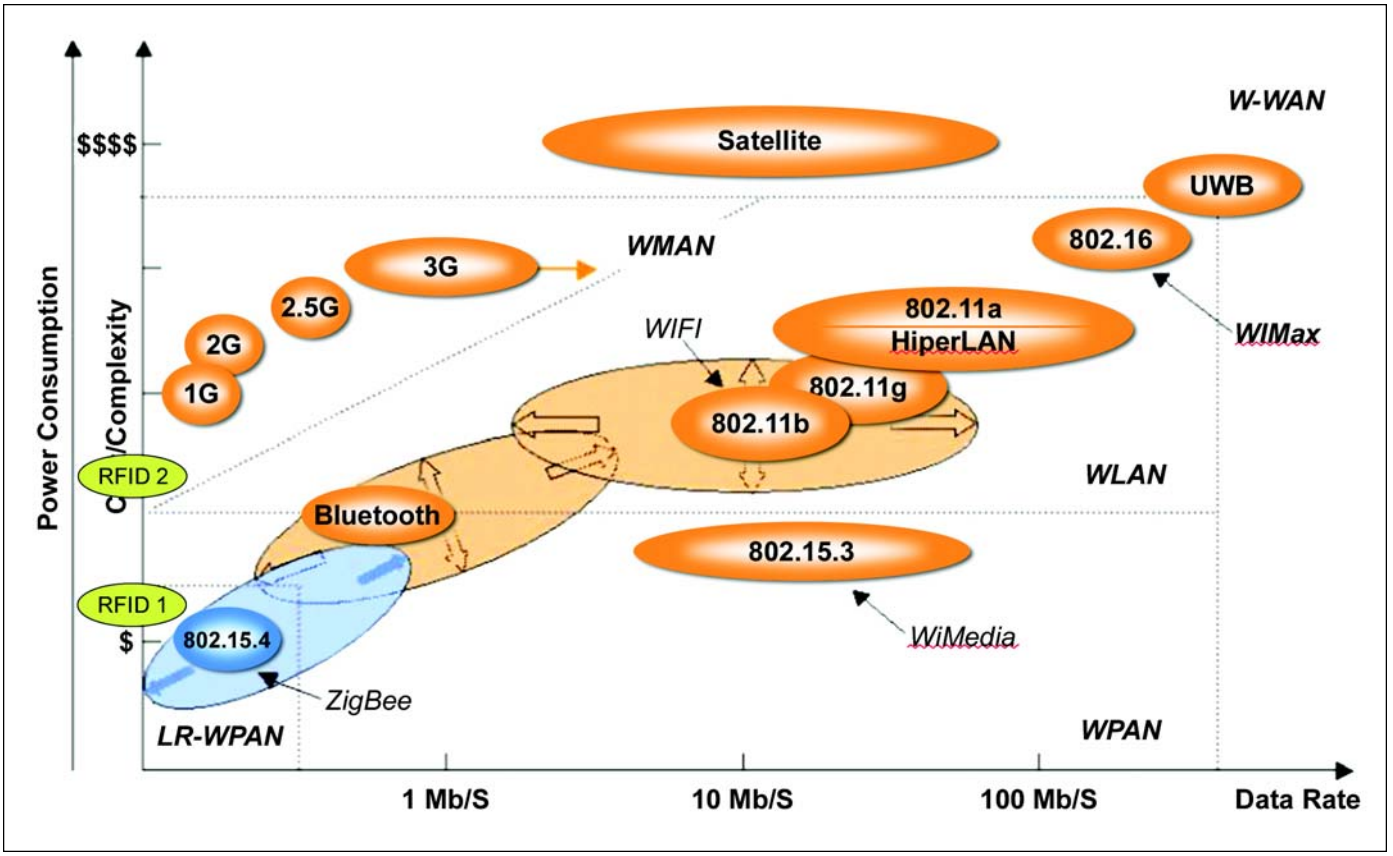

Figure 3. Wireless standards and technologies now in use.

abling remote electronic capture of process data (e.g., remote validation protocol execution via wireless tablet PCs)
- electronic product authentication and electronic pedigree documentation
- improved equipment availability and reduced maintenance costs through proactive condition monitoring, for example, implementing wireless vibration sensors to indicate system malfunctions
- improved flexibility for quick process unit changeover
- reduced downtime and costs for wireless sensors on skids by eliminating the need to connect instruments and computers to field networks
- faster process changes through reconfigured operations
- better tracking of clean-in-place components
- improved utilization of process equipment through more precise measurements of process variables such as temperature and pressure
- greater efficiency in enabling PAT solutions

Maintenance and Infrastructure Management

- eliminating wiring related costs in upgrading or installing control systems
- improved plant safety and security through proactive perimeter monitoring, Weapons of Mass Destruction (WMD) detection, and personnel tracking

Although it is quite feasible for each department to present a strong business case for using wireless networks in its own operation, these considerations must be made at the enterprise level. Data integration, process integration, and knowledge sharing are some key performance enhancers in pharmaceutical production. Process, security, or logistics needs must be evaluated in the context of the overall enterprise strategy.

A company whose strategy is driven by reducing costs might want to deploy wireless vibration sensors to determine when assets are not operating optimally. They would then look for savings on maintenance in the bottom-line. Other applications for wireless sensors might include temperature monitoring of product in storage and transportation.

In contrast, a company whose strategy is to get to market faster, reliably, and securely, might find that the added cost of an RFID product tracking system would improve their competitive position. According to a Gartner report, "industries with the greatest opportunities to use RFID include retail and aerospace and defense, while the healthcare, logistics, and pharmaceutical industries will adopt RFID the fastest."[1]

The US Food and Drug Administration (FDA) has stepped up its efforts to improve the safety and security of the nation's drug supply by promoting the use of RFID technology. The FDA launched this effort by publishing a Compliance Policy Guide (CPG) for implementing RFID programs that are designed to enhance the safety and security of the drug supply. This action continues the FDA's commitment to promote the use of RFID by the US drug supply chain by 2007.

The FDA believes that anti-counterfeiting is a major benefit of RFID. However, the benefits of RFID go well beyond the fight against counterfeit drugs. The pharmaceutical industry relies upon the integrity of many forms of data throughout the process of drug trials, manufacturing, distribution, and retail sale. RFID's ability to uniquely identify each item and securely capture data without line-of-sight throughout the supply chain has many benefits in the pharmaceutical industry.

RFID in the pharmaceutical supply chain is seen as a technique to enhance patient safety and security and addresses emerging regulatory requirements like Florida's anti-counterfeiting law. Preventing drug counterfeiting, for example, calls for drug products to carry a genealogy of their history. With drug counterfeiting on the rise, pharmaceutical RFID security is critical.

Implementation of wireless technologies also aligns with the FDA's efforts to increase efficiencies within the development and manufacturing sectors under their 21st Century Initiative as well as Process Analytical Technology (PAT). Not to be mislead by the name, PAT allows pharmaceutical manufacturers to optimize the manner they use to manage their plant assets to produce specific drugs with the objective of reducing the price that the consumer pays. PAT also allows pharmaceutical manufacturers to apply new technologies such as advanced process control and wireless networks.

Managing Secure Integration in a Regulated Environment

The greatest threats to wireless security are not from malicious interference, but from otherwise well-intentioned people engaged in sloppy networking practices, such as not changing passwords according to policy, using obvious passwords such as initials, adding or deleting devices improperly, and any number of other lapses. Wireless networks are also subject to interference from other non-malicious factors, environmental or accidental Radio Frequency (RF) noise, broken RF equipment, dynamic changes in the characterization of the RF site, and the range on non-compatible RF devices generally available.

And as wireless usage expands, competition for the wireless spectrum within and around the plant will become the major issue. One network user might be taking wireless process measurements from a temperature transmitter. Another person in the same plant might be running a wireless video camera for perimeter security. A third might be running an RFID inventory tracking application. Because they are in different departments and locations and doing different things on different protocols, they might think they are isolated, but in reality, those radio waves are co-mingling creating tremendous potential for performance problems and mismanagement.

Coordination of diverse wireless needs is critical, but not likely to emerge by consensus. If each department wanting to deploy a wireless solution had to check with every other department to see how their wireless activity would impact them, there would be gridlock. There must be a higher level framework that respects what people need to do to perform their roles and responsibilities in the context of the business strategy and the related job responsibilities. At the same time, customers must have assurance that if they implement select technologies and practices that conform to company policy they will enjoy reliable, secure, validated network operations.

When considering the use of wireless technologies in the pharmaceutical industry, security and validation are at the forefront of most people's mind. Security is mandated by the FDA's 21 CFR Part 11 regulation on electronic signatures/electronic records. Because the wireless technology typically does not interface with the product directly, validation issues would be comparable to wired network technology. However, there is a need to assure that interference and security are managed.

Financial reporting and disclosure regulations required by the Federal Sarbanes-Oxley act, and the use of Web-based interfaces also have increased the need for secure access control to address compliance and liability concerns.

Managing System Policies and Standard Operating Procedures

The policies and Standard Operating Procedures (SOPs) in place for wireless networks must define all methods using, sharing, and securing the available bandwidth. This has implications for planning, implementation, operation, maintenance, and expansion. Policy management and validation also tie into the end user's existing IT requirements – one company might have IT policies in place that are very different from another in the pharmaceutical industry. The system must be designed to comply with corporate requirements for activities like reporting errors, observing network behaviors, and performance based on that information. It must cover every aspect of the operations, from initial configuration to ongoing optimization.

Commissioning and qualification of the wireless network would be comparable to commissioning and qualification of any network, but with added emphasis on security and interference. Interference would be addressed first during the RF site survey, which uses scientific tests to measure RF in the plant and in the local area surrounding the plant.

Additional security and RF interference testing also must be built into routine maintenance procedures to account for changing internal and external conditions. Events ranging from a microwave oven at a new convenience store to full-blown competition for the RF spectrum from a new plant being built next door all represent potential RF and security threats that must be detected and may require re-validation and re-qualification.

Policies and SOPs that meet regulatory requirements also must be in place for handling problems. Once the system detects interference, for example, what does it do? Will it reroute traffic, change frequencies, or reconfigure antennas to be active or inactive? Some of

the options depend on the capabilities of the technology, but within that framework, policy and network management is necessary to guide implementation and network operation.

Performance, availability, and utilization are also among the reporting criteria covered by systems management and also must be considered when validating. Policies, such as alarm alert handling which dictates alarm related operator actions, are part of the systems management function.

Managing the System Architecture

Optimum execution of any enterprise-wide policy requires a network architecture that can accommodate technology of every possible network vendor, emerging standards, regulatory guidelines, and best wireless integration practices. The architecture must be based on a secure model covering authentication and role-based access control. This should provide for common addressing, routing, messaging, and device management. The architecture also should provide consistent data structures, storage, and reporting, and a common point of configuration for all business rules and workflow.

Figure 3 illustrates the array of standards now impacting wireless communications. Some have been developed by industry standards groups comprising vendors and users. Bluetooth and WiFi are two of the better known, yet these are seen as better for voice and graphics applications. ZigBee is a low-power, slow-data standard that has many supporters for remote monitoring. Predictable, long-lasting power is key for wireless monitoring, and ZigBee supports battery life of 1,000 days or more.

Members of IEEE, ISA, and WINA are currently working together on standards that they hope will gain acceptance by the International Electrotechnical Commission (IEC). Just over a year ago, a new ISA standards committee, ISA-SP100, was formed to further standards and technical documentation in the automation and control arena. Project teams have formed to focus on issues such as

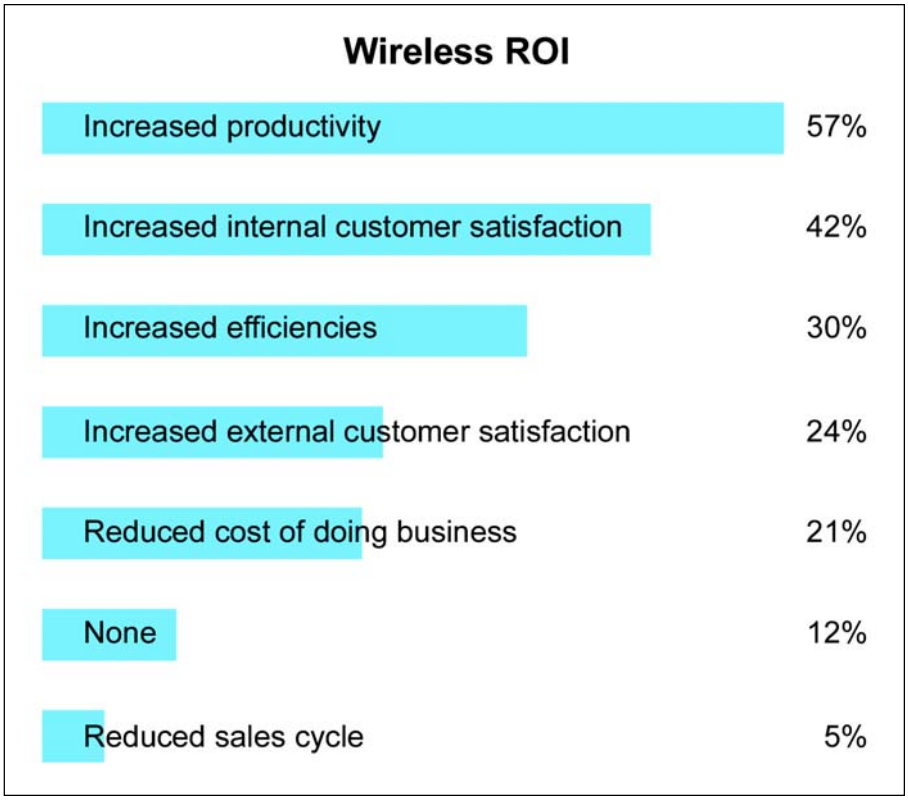

Figure 4. Measuring wireless benefits.[5]

education, guidance documentation, and interoperability of sensor networks within the industrial environment.[4]

Managing and Validating System Traffic

Unlike wired networks, which can be fairly well isolated, closed by function or protocol and kept independent of other networks, wireless signals cannot be managed physically. Wireless traffic is controlled by agreements and rules, requiring buy-in from everyone with access to the bandwidth spectrum.

The data may transmit across the same virtual wire or air link, but would not necessarily have to be interspersed with like data. A process packet and an Internet Protocol (IP) packet would not necessarily have to be on the same link. Instead, rules could limit access to process data to users on the process side of the house; or transmit data to receivers on the same side. The company has the power to dictate what goes where and to configure the rules.

One key to flexible, secure operation is the ability to validate any packet of information moving across the network with a recognized and authorized sender or receiver. This type of identity management can be done by a number of methods including certificates and tokens. Both can authenticate devices with a unique identifier. Management must determine how those certificates are assigned, distributed, and evaluated, and what privileges that identifier would have. They must define exactly how to treat each user or device as an object with its own unique properties or attributes. This is a much better method for assigning a unique identifier than IP or other alternatives. This is a well understood technology, but its effectiveness decreases significantly without enterprise-wide coordination and validation of wireless applications.

From a technical and practical standpoint, there must be a single point of access to the whole network of networks, using a common network and a common lexicon.

Managing System Growth

From a network management perspective, it shouldn't matter if signals transmit across wires or not. The network management center should see the wireless path as just another network

that must be managed for performance and security. But today, and probably for many years to come, wired and wireless networks will likely be managed by different technology. Even though IT and telephone networks may be managed by a company's IT organization, for example, they typically use different management systems. Voice over IP is only now driving the need for integrated management and validation of IT and telephone systems, even though these technologies have been evolving for years.

Even though wireless technology is clearly in a transitional phase, it is highly unlikely that there will ever be a standard wireless protocol and frequency. Protocols and frequencies are optimized based on very different application requirements and vendor technologies. The requirements for power management, distance, site characteristics, bandwidth, cost, and security will always result in the need for a wide range of technologies, standards, procedures, and excellent validation methodologies.

What is needed is an integrated, yet flexible network management strategy that can deliver benefits today while adapting to businesses and technologies as they evolve and change.

Solution for Wireless System Infrastructure and Management

Thanks to standards and innovation, wireless technologies offer a compelling mix of cost and performance that will spur adoption throughout the enterprise. "When asked how their organization would measure the return on wireless investments, respondents listed increased productivity, improved (internal) customer satisfaction, and reduced expenses/costs of doing business most frequently - *Figure 4*."[5]

Moving beyond prototyping to control-a future at which some companies in other industries have already arrived-requires an overarching framework to accommodate and apply multiple wireless technologies. Since there is great heterogeneity to the applications and no "one size fits all" wireless technology solution, monitoring, management, and security must span the entire enterprise. This will ensure the most efficient use of resources, while allowing the disparate applications to share the spectrum within the context of their importance, time sensitivity, and mission criticality.

Like the networks themselves, such a regulated wireless infrastructure must be evolving, dynamic, and flexible. This environment demands an integrated operating approach that will ensure that wireless installations will be scalable, secure, and extensible. Solutions must include architecture and management software, performance monitoring and reporting, and security management as a single solution - *Figure 5*.

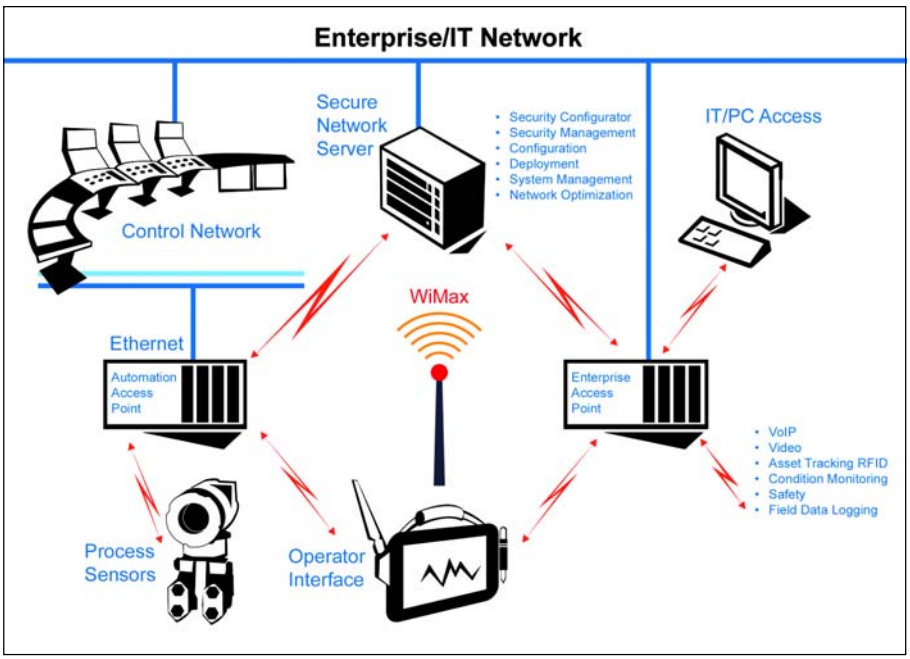

Figure 5. Secure wireless architecture for the plant network.

Managing Implementation

While implementing a management infrastructure of this sort requires several months of preliminary cross-company planning, implementation of the technology itself can usually be done in one or two weeks. Few companies have the resources to maintain staff necessary for initial implementation, especially because the demand for specialists with relevant skills is very high. Companies that do not have the resources typically required to implement a managed wireless network may find outsourcing to one of the emerging specialist firms to be a cost-effective solution.

The following is a check list that process manufacturers should consider when assessing wireless needs and designing a wireless network system that is consistent with their wireless strategy, policies, and quality system:

- Survey the entire company to determine where wireless technologies can best support your business strategy.
- Create an enterprise-wide policy that will control wireless deployment.
- Design an architecture that will achieve these goals effectively.
- Conduct an RF site survey to identify potential sources of RF interference and locate wireless communications devices, both internally and externally to the plant.
- Work with a validation specialist with experience in wireless technologies and networks.
- Select and purchase hardware and software that is most cost-effective, proven, and scalable.

- Develop a prototype in an area with high ROI potential for immediate payback such as cycle time reductions or counterfeiting exposure for high profile drugs.
- Build requirements and design documents for a pilot wireless prototype application running separately from the process for system validation.
- Pilot a project for integration to an existing application.
- Integrate to the existing business and operations systems.
- Measure and evaluate ROI effectiveness of application.
- Collect lessons learned, measure cost-effectiveness of improvements, reassess the strategy, and plan next steps, including additional sites, plants, and global solutions for a rollout.
- Conduct ongoing monitoring, maintenance, support, and optimization services, and incorporate relevant security, regulations, standards, and technologies as they emerge.

Summary

Technology is enabling a vast number of wireless capabilities across the pharmaceutical enterprise. The nature of wireless applications requires a high level of technical understanding for implementing and validating wireless network applications.

As a result, it is important to establish a strategy and plan before going forward with wireless just for the sake of going wireless. The plan should include benefits that will be gained from using these new technologies whether tangible or intangible. Some of the steps and guidelines for implementing wireless include working with an experienced and knowledgeable company and working with a wireless infrastructure and plan that will incorporate present and future wireless needs. The infrastructure needs to be flexible enough that new wireless technologies, methodologies, and new regulations can be easily incorporated. The bottom line is that there is a potential wireless explosion on the horizon due to the enormous benefits that can be gained from using this technology and companies need to be ready to validate and implement.

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Process Solids Handling Approach for Multi-Product Bulk API Facility

by Prashant Desai and Pramod Biyani

This article presents a case study describing the approach taken for handling process solids for a multi-product bulk API Manufacturing Facility.

Introduction

Multi-product bulk Active Pharmaceutical Ingredient (API) manufacturing facilities are becoming the norm in the industry. This is largely driven by the fact that only a small percentage of APIs in development make it to the market. Therefore, a pre-investment required for a dedicated facility is very risky. A multi-product facility spreads the risk over multiple products under development and still allows manufacturing of commercial quantities of API, once the product is close to being approved in a relatively short amount of time.

From the design perspective, multi-product facilities introduce a set of complex challenges – among them the selection of a process solids handling scheme. By its very nature, a multi-product facility must be designed to handle poorly-flowing materials. The containment level required to handle the potential solids material in the facility is another important consideration. Good judgment is required to set the containment level for the facility, based on the envisioned characteristics of the potential products and intermediates to be handled in the facility. Containment level is determined by the Operator Exposure Limit (OEL) and/or other toxicological properties of the solids material. Table A describes various containment levels and their implications for the design of solids handling equipment.

This article presents a case study describing the approach taken for handling process solids for a multi-product bulk API Manufacturing Facility. This facility is designed as a flexible, multi-product facility with the capability of handling materials requiring up to Containment Level 3 (Operator Exposure Limit of 10 to 100 micrograms of airborne dust per cubic meter of air over an eight hour time weighted average). The other basic design objective is to comply with the latest GMP practices for the manufacturing of bulk active pharmaceutical ingredients. Ease of cleaning and validation are important considerations in any multi-product facility. All aspects of solids handling will be covered, starting from the dispensing operation in the warehouse, in-process solids handling, and final bulk product packaging. Equipment design and operational considerations will be discussed, not only to meet the design containment level, but also to comply with the latest GMP practices.

Facility Overview

An overview of the process solid materials handling system in the Process Building and Warehouse/Dispensary Building is presented below.

Process Building

The process building is configured into seven "wet" processing (chemical synthesis) trains, seven "dry" processing (isolation) trains, and

Table A. Containment levels and associated design options.

Level	OEL Range	Design
1	> 1000 μg/m^3	General room ventilation. Conventional open equipment with local exhaust ventilation (LEV).
2	100 to 1000 μg/m^3	Semi-closed to closed material transfers; laminar flow/directionalized laminar flow, engineered LEV.
3	10 to 100 μg/m^3	Transfers using direct coupling and closed systems, selected use of unidirectionalized air flow booths.
4	1 to 10 μg/m^3	Totally enclosed processes; transfers using direct coupling; barrier/isolator technology.
5	< 1 μg/m^3	Isolator technology; remote operations, fully automated.

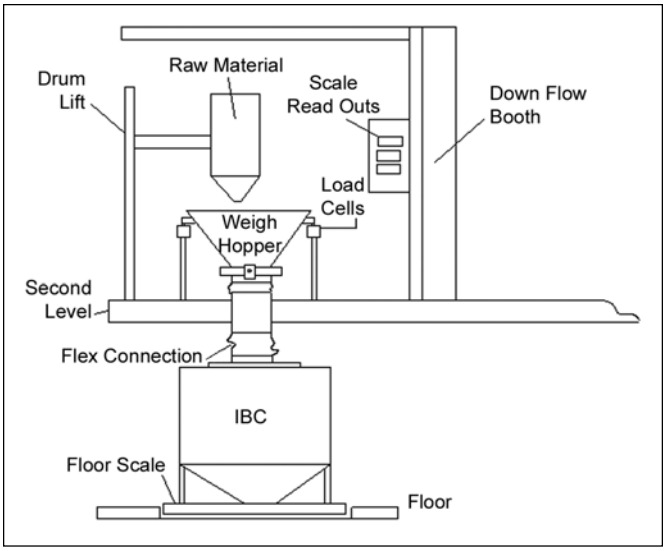

Figure 1. Dispensary stack up.

the infrastructure to support both areas.

Each wet side train consists of a set of reactors and receivers, provision for solids and liquid charging, a vacuum source, and all attending support facilities (jacket systems, solvent/process transfer piping, and utilities). Reactor sizes range from 8,000 to 20,000 liters.

Each dry side train consists of a crystallizer followed by a centrifuge and a dryer, or a combined filter-dryer. Three milling rooms are provided on the dry side for size reduction purposes, typically used only for the final bulk API.

The major features of solids handling equipment in the Process Building are:

- contained charging stations by which the solids are introduced into the process main reactor without operator exposure
- packout stations at the dryers and mills where the products and intermediates are containerized
- intermediate packout and charging provisions between the centrifuges and the dryers which allow interruption of the process flow to remove material and reintroduce it into non-consecutive systems

Warehouse/Dispensary

Incoming raw materials are subdivided and packaged for introduction into the process in the dispensary, located in centralized warehouse. Incoming raw materials, which may arrive in any of the several types of packages (bags, bulk sacks, drums, and totes), are weighed into stainless steel Intermediate Bulk Containers (IBC) of various sizes ranging from 500 to 1500 liters. These containers are the primary vessels used to convey pre-weighed charges of solid process material to the manufacturing operation.

The Dispensary is a two-level facility designed to dispense certain raw materials in Level 3 containment conditions. However, most of the raw-materials do not require this level of containment. Operational measures also are taken to handle certain Level 3 raw materials in the dispensary**.** Raw materials are weighed and dispensed on the floor above and collected into an IBC, located inside a downflow booth on the floor below. Three of these setups of varying capabilities are provided to handle expected throughput and wide spectrum of materials packaging including bags, drums, totes, supersacks, etc. Figure 1 shows a schematic representation of one of these setups.

In addition to the weighing (e.g., bench and floor scales), transporting (e.g., pallet trucks), and conditioning (e.g., delumper) equipment used in the dispensary itself, the warehouse also contains an IBC washer, full and empty IBC staging areas, and shipping and receiving areas for supplying and returning containers to/from the Process Building.

Process Building Operations and Material Flow

To meet the containment requirements, it was imperative to maximize the use of closed systems and use multiple orthogonal containment strategies (strategies that work independently of each other) where process connection/disconnection is made, thereby potentially exposing the product into the external environment. This section discusses the operation and features of the solids handling equipment in the process building.

Process Building Materials Receipt

The materials from the central site dispensary are received into the process building in an in-process staging area. The materials are in IBCs that are pre-weighed in the dispensary and bar coded in order to avoid mix-ups. The materials are staged as batch "kits" (sets of containers filled with all of the solid material required to produce a single batch of intermediate or product) and held until needed on the charging floor.

Figure 2. IBC docking station.

Material Transport

The materials are transported throughout the building by electric forklift or by hand pallet truck. The movement from the staging area to the production area requires the materials to be placed in an air lock to enter any clean areas (centrifuging, drying, and milling) and to be delivered directly to any other use areas.

Material Charging Floor

When batches of materials are delivered to the charging area on the top operating level, they are staged in the staging area in front of the appropriate charging station (e.g., for reactors, mills etc.).

Reactor Charge Booth Operation

The main reactor in the process area is served by its own solids charging station, which is located on the floor above the reactor. A fixed chute provides the route for conveying the solids from the IBC docked to the station to the reactor. Each station can charge the contents of an IBC to its reactor or can be converted to charge from individual drums. Either operation is designed to be effected in a contained manner. The preferred container is the IBC. However, the design is flexible to allow the use of drums in special cases. Each charge station is enclosed in a down flow booth. Figure 2 shows an IBC docking station used for reactor charging.

The booth is set up with a docking device to receive the proper container for the charge (IBC or drum). Then the materials are brought into the booth. The IBC is docked or the drum is placed into the inverter.

In the case of an IBC, the dock station is actuated and the IBC is discharged. Following discharge, the IBC is disconnected and undocked, weighed for a check tare, and sent to the soiled IBC holding area.

In the case of drums, the pre-weighed drums are charged and the empty drums are sent to the waste disposal area for removal.

Dryer Discharge

The packout stations below the dryers are designed for the contained discharge of dried material into IBCs. A contained IBC filling head is used to maintain Level 3 containment during filling. The dryer discharges via this IBC filling head into an IBC.

Clean and empty IBCs are shipped from the warehouse. The IBC is stored in the in-process staging area when it arrives. When needed, it is placed in the dryer floor air lock to be picked up with a clean hand truck. The IBC is then tared and placed below the filling head. The filling head is then lowered to mate with the IBC and dryer discharge is started. Once filled, it is weighed and staged for feeding to the mill.

Milling

An IBC is placed on the docking station above the mill, and a drum is placed in a drum packout booth below the mill. The drum packout head incorporates a continuous liner system - *Figure 3*. The milling is started and the drums are changed out as required. The drums are tared before loading and weighed after loading. The filled drums are transferred to the shipping area to be sent to the warehouse. The empty, soiled IBCs are sent to be washed in the warehouse.

Figure 3. Drum packout head with a continuous liner.

Charging of Wet Cake

The charging of wet cake into stainless steel drums is only required in an upset condition, such as a batch problem or a dryer malfunction. This is done using a portable drum packing head with fume and dust extraction. This also means that any charging to a dryer from drums only be done for similar reasons. Charging the stainless drums to the dryer is accomplished by removing a spool of the centrifuge charge chute, placing a lip seal on the open end of the chute, and charging drums via a portable drum inverter. The drums will be fitted with cones, which mates with the lip seals. A portable extract hood will be provided at the point where the drum cone meets the lip seal.

Small Scale Additions

Small additions of dry ingredients to the process vessels (e.g., reactor, crystallizer) are performed by using containers equipped with split-butterfly valves. The active butterfly section is attached to the process vessel and the passive butterfly section is attached to the container. The pre-weighed

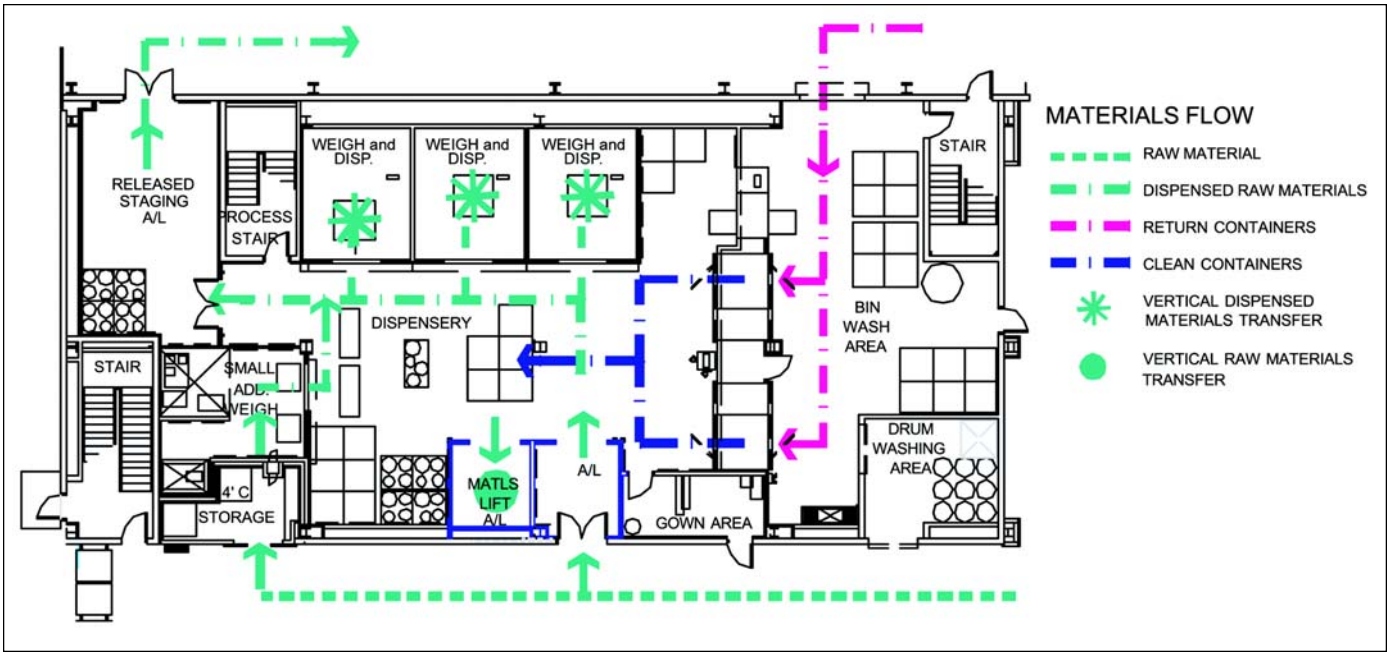

Figure 4. Warehouse dispensary layout and material flow.

container, received from the dispensary, is manually locked onto the active half of the split-butterfly valve on the process vessel. The split butterfly valve is then opened to discharge the material and the empty container is returned to the warehouse for cleaning.

Cleaning

The portable docking stations are taken to a wash area in the process building and cleaned along with the used drum cones. The IBCs are transported to the warehouse for washing and clean storage. Clean IBCs are then filled in the dispensary or delivered empty to the process building as needed.

Warehouse and Dispensary Operations and Material Flow

The key to implementation of the process solids handling scheme described above is the process material warehouse operation. The basic premise of the solids handling design is that all solid process raw materials will be prepared in a central dispensary located in the warehouse. An additional stipulation is the use of IBCs as a primary means to transport process solids from point to point. This requires that facilities be included in the warehouse to clean and store these containers. This section discusses the operation and features of the warehouse and associated dispensary.

Material Flow and Layout Considerations

The warehouse is designed to service the process building. Its function is to receive, sample, inventory, and dispense raw materials destined for use in the process building, and to inventory and ship out the products manufactured in the process building. Raw materials are received in drums, totes, and bulk bags of assorted sizes. Provisions are made to handle certain materials under Level 3 containment condition in the warehouse dispensary.

Personnel and material flow within the warehouse and dispensary is to be conducive to GMP. Traffic flow is arranged such that pass-through handling is used wherever appropriate (e.g., IBC washing, dispensary materials flow, etc.). Where not feasible, traffic flow is patterned such that raw materials and finished goods do not follow common paths during handling. Similarly, non-qualified materials bound for quarantine and qualified materials being removed for use follow different routes.

Within the warehouse, materials enter through the receiving dock and exit through either the dispensary or the shipping dock. Innocuous waste products (outer packaging, wrapping etc.) are disposed through the trash compactor. Non returnable primary packaging, which may contain chemical residue, are decontaminated according to the local requirements before being disposed of (resale, incineration, compaction etc.). Returnable primary containers are washed and decontaminated before being stored prior to being returned to the supplier. Incoming materials, outgoing materials, and waste products remain segregated at all times.

Material flow requirements within the dispensary also are similar. Components for manufacturing kits and clean IBCs enter the dispensary via a materials airlock. Waste packaging materials generated within the dispensary are bagged and tagged for disposal. Materials assembled into manufacturing kits are transferred from the dispensary through the materials airlock and staged at the dispensary shipping dock for transfer to the process building. Incoming materials, outgoing manufacturing kits, and waste materials remain segregated at all times. Primary containers are treated in much the same way as in the warehouse.

Secondary containers (IBCs) leave the warehouse filled as part of manufacturing kits from the dispensary shipping dock. The empty, soiled containers are returned to the warehouse at a separate dock where they are staged for cleaning.

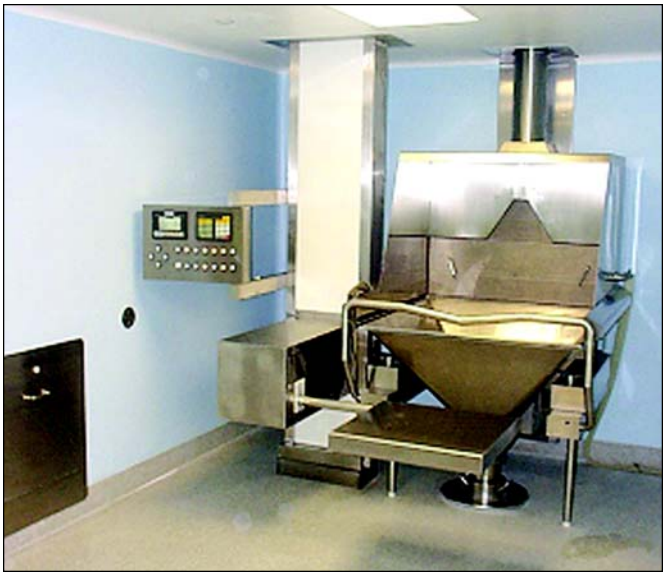

Figure 5. Weighing funnel located at the upper level.

The IBCs pass through the washer before entering the warehouse for clean container staging.

Dispensary Operation

Dispensary personnel enter the dispensary gowning room in their plant whites. They complete their gowning procedure, including a one piece Tyvek suit with boots and gloves, and proceed into the dispensary. For emergency situations, such as a break in containment, battery operated HEPA filtered breathing air packs or other appropriate personnel protection devices are available.

Raw material containers are transferred from the dispensary staging area into the dispensary airlock. Dispensary personnel retrieve the containers from the airlock and transfer them into the appropriate weigh booth via the clean corridor. The containers are positioned on the upper level to discharge their contents through the floor into IBCs below. The IBCs are located on weigh stations, which indicate and/or control the flow of material into them.

Weigh Booth Operation

Supersacks are handled in a weighing station equipped with supersack handling and discharging equipment. The supersacks are brought into the weighing station by forklift truck and positioned above the discharge hopper.

Drums, bags, and cardboard boxes are handled in one of the three weighing stations equipped with a weigh funnel - *Figure 5*. Drums are mated with a drum cone and attached to a fixed drum lift/inverter before being tipped into the weigh funnel. Sacks and boxes are tipped directly into the funnel. When the correct weight is registered in the funnel, the contents are released into the IBC below.

Small Scale Dispensing

A separate small weigh room is located in the dispensary area for dispensing small quantities of dry ingredients into a container fitted with a split-butterfly valve. This operation is performed under a laminar flow booth equipped with a bench weigh scale.

Container, Pallet, and Appurtenance Washing and Storage

Used IBCs are returned to the Warehouse Building from the Process Building and are unloaded onto the washer receiving area and transferred into the IBC wash area. IBC washers are utilized to clean the IBCs inside and outside. Containers are loaded onto the in-feed conveyor of the washer and are fed automatically into the washer. The washing cycle is validated and may vary according to the material to be removed. At the completion of the washing cycle, the containers are ejected from the washer cabinet and are transferred by electric forklift truck or pallet jack to the clean pallet staging area.

Soiled plastic pallets are staged, ready for washing close to the in-feed of the pallet washer. They are manually loaded onto the washer in-feed. Pallets are transferred through the washer and drying section. Upon exiting the drying section, pallets are removed from the washer by hand and stacked for transfer to the pallet staging area.

Conclusion

Solids handling is an important aspect of the overall multi-product bulk API facility. IBCs are a perfect choice to transport process solids material in these facilities, as they can easily handle the range of solids material typically involved. IBCs also can be fitted with suitable loading and discharging systems to not only handle poorly-flowing materials, but also to meet varying level of containment requirements. Integrating suitable personnel and material flow features, conducive to operation and GMP requirements, into the overall facility layout is another key to successful design.

About the Authors

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Using Cycle Time Analysis to Enhance Operations and Improve Yield

by Robert F. Dream

This article analyzes the necessity of a pharmaceutical expansion project or new plant by attempting to understand the business and the production capability of the firm.

Introduction

As pharmaceutical manufacturing sites grow and production demands increase, the question will arise: How should we best use existing operations to meet increasing demand? Is it time to procure a new line or build a new facility? Challenges will increase as manufacturing spans to multiple sites, numerous countries, and many regulators with different regulatory backgrounds.

Project selection takes on different faces in different corporations. While the overall goal of any project is to improve customer satisfaction and profitability, some projects will focus on industrial processes and others will focus on commercial processes. From the author's point of view, projects must be linked to the highest levels of strategy in the organization and must be in direct support of specific business objectives.

The project(s) selected to improve business productivity must be agreed upon by both business and operational leadership, and someone must be assigned to "own" (be accountable for) the project and to execute the project. In this article, we will introduce a means to analyze the necessity of a pharmaceutical expansion project or new plant by attempting to understand the business and the production capability of the firm before diving into building a new facility. The following will be considered: Yield Rate, Cost of Poor Quality, Capacity, Customer Satisfaction, Internal Performance, Design, and Supplier Quality.

In order to understand the product(s), consider what and why a project is proposed. What is going to be manufactured and what capacity increase is needed? Establish if the product(s) is being manufactured and if an increase in capacity is needed and/or additional manufacturing capability of new product(s) is the issue. This will provide a road map for what we need to study and what data we have to collect, and how to analyze the data.

If the product(s) exits, then we have to col-

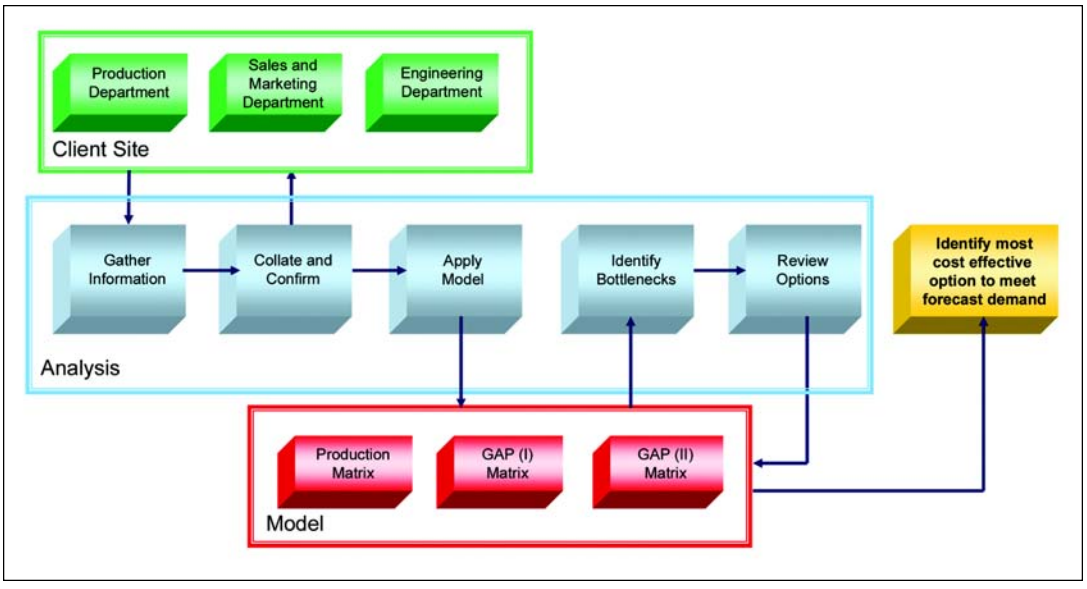

Figure 1. A flow chart depicting interview, data collection, and analysis supporting Phase 0, Phase I, and Phase II of the S⁴.

lect marketing data, manufacturing data of existing and new equipment, and a marketing forecast for now and where the firm wants to be in future years (say three, five or 10 years). If the product is new, existing production data will be replaced with pilot plant data and pilot plant equipment data will be renewed instead of existing equipment data. By selecting a format using Excel and/or another data base platform, the analysis will begin by looking at the bigger picture, and produce options for the path forward. The process here is a mini-Six Sigma process localized to the project(s).

The following discussion will refer to "the Capacity Enhancement Tool," which is based on utilizing "Six Sigma Smarter Solutions (S^4)," i.e., Phase 0: Deployment Strategy; Phase I: Measurement; Phase II: Analysis; Phase III: Improvement; Phase IV: Control.

When a project is funded, it is based on the firm's management decision that the company has data supporting a capacity increase or change. The Capacity Enhancement Tool is an integrated collective of chosen project(s), collected data from marketing, operations, and engineering functions. The data is used to support the definition of cycle time and required for the analysis to determine the optimum solution to implement the project as an answer to the need of the marketability of the product in its best possible way. The results of the process must be implemented by choosing one or more of the solutions produced. Then, further developing/refining the choice to a final design for the project.

The following definitions will help lead-in to the process:

Cycle Time

Cycle time is the total time from the beginning to the end of the process, as defined by you and your customer. Cycle time includes process time, during which a unit is acted upon to bring it closer to an output, and delay time, during which a unit of work is spent waiting to take the next action.

In a nutshell, cycle time is the total elapsed time to move a unit of work from the beginning to the end of a physical process. (Note: Cycle time is not the same as lead time).

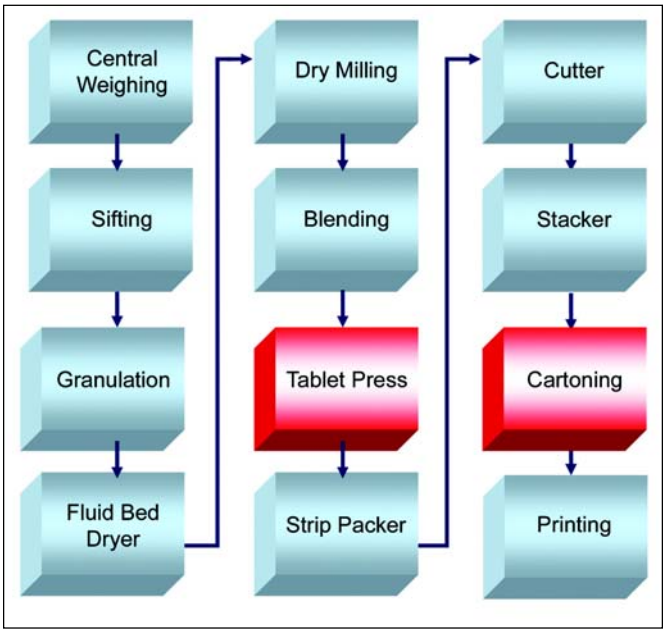

Figure 2. Material Flow Diagram of process line investigated using the GAP(I) and GAP(II) matrices. Pinch Points are highlighted.

Some of the most important data in any line balancing project is the cycle time. In a paced line, the cycle time is often meant to be the time it takes before the product leaves a workstation and moves to the next one in the line. By this definition, the cycle time is the same for all workstations in the line. However, this definition is often too restrictive: in many real lines, it is desirable to have a certain "reserve" of time at the workstations at the end of the line so that possible perturbations (e.g., equipment downtime) can be absorbed easily by those workstations.

Optimum Line (OptiLine) defines the cycle time as the work time that should be spent on a workstation. As such, the cycle time is defined for each of the workstations separately and can differ from one workstation to another; in particular, it can decrease toward the end of the line. OptiLine's optimizing algorithm is capable of taking the varying cycle time into account.

Because the cycle time is allowed to vary among workstations, all the workstations and their respective cycle times must be fixed before the optimization can take place. During optimization, the cycle time is taken into account in the following manner. Because the objective of the optimization is to balance the workload among workstations, the optimizing algorithm aims to assign operations to workstations in such a way that the ratio of the work time and the cycle time be as equal as possible across all workstations.

For example, suppose that there are two workstations in the line, and the first workstation's cycle time is double the cycle time of the second workstation. The optimizing algorithm will attempt to assign the operations such that the first workstation will have double the work time of the second workstation. In cases where there are workstations with several operators, the work time on a workstation is taken to be the longest work time among all the operators assigned to the workstation.

Note that in real-world applications, it is usually impossible to find an assignment of operations to workstations that would perfectly match the cycle times. As a consequence, if the cycle times specified for the workstations are too tight compared to the amount of time necessary to carry out the operations, the cycle time can be exceeded on some or all workstations. In that case, it may be necessary to add workstations (or operators) and rerun the optimization in order to find a feasible solution. Conversely, if the work times obtained in a solution are way below the available time, it may be possible to eliminate workstations (or operators) and increase the efficiency of the line.

GAP Analysis

The GAP analysis is a process of determining and evaluating the variance or distance between two items' properties being compared.

- GAP(I): Comparing the state of a station (Equipment/System) at present condition vs. the needed state.
- GAP(II): Comparing the state of an integrated line/facility

at present condition vs. the needed state. This is an integrated situation of multiple equipment/systems analyzed individually in GAP(I).

The GAP analysis is the fastest, most efficient way to assess how your quality system measures up to the requirements of a particular standard and to define the logical next steps in the implementation/registration process.

- Assess compliance to the standard.
- Identify missing elements required by a standard.
- Determine if resources are adequate to complete the implementation/registration project.
- Identify training needs.
- Define how best to proceed with registration or implementation.
- Determine how to address the requirements of a standard.
- Assess the efficacy and completeness of records and documented procedures.

Process

Project Definition

- Understand project background and your objectives.
- Prepare an agenda of evaluation activities.
- Determine the method for reporting for gaps.

Project Implementation

- Tour the facility.
- Conduct interviews with key process owners.
- Review existing documentation.
- Conduct internal audit of all major areas and processes.
- Review compliance with applicable federal, state, and local regulations and requirements.

Project Conclusion

- Deliver Gap Analysis report to management (optionally, deliver findings in an executive presentation).
- Provide technical support on corrective action for report findings.

The duration of the Gap Analysis depends upon such variables as the size of the organization, geographical factors, organizational complexity, and the required level of detail. Generally speaking, the process will vary depending on the depth of analysis required. The final schedule will be determined after the project definition phase.

At the completion of the interview and inspection process, deliver a professionally written report detailing the findings and suggestions. Also, conduct an executive presentation if you prefer a more interactive review of the findings.

The only way to know if your existing processes are giving you the highest return on investment is to have a Gap Analysis performed.

The Capacity Enhancement Tool

The Capacity Enhancement Tool is based on Cycle Time Analysis and is used to examine process unit operations across a wide variety of different biopharmaceutical/pharmaceutical plants and identify the equipment items in the line that are acting as a constraint to current or forecasted output. Having identified the pinch points, the tool can be used in a predictive manner to quantify how modifications to the process line can result in improved capacity and can be used to minimize the capital expenditure required to reach required capacity. The tool also can be used to indicate how existing integrated equipment trains can be used more effectively to increase output (product optimization).

The analysis is applicable to any process: Active Pharmaceutical Ingredients (API), Oral Solid Dosage Form (OSD), Biological, Sterile Dosage Form, Ointments/Creams/Topical, Suspensions, Liquids, etc. Case studies (projects) have been performed to represent all of the above manufacturing forms. This analysis also has been applied to complex multi-product facilities. This tool recently has been applied to increase the capacity (by 50%) on an OSD, multiple Stock Keeping Unit (SKU), multiple country product for a confidential client. It also has been successfully utilized to carry out worldwide product optimization for a second client of fill/finish pharmaceuticals product manufacturer. The third example is an optimization of multiple products across multiple dosage

Client Products			FORECAST									
SKU	(TABLET x TABLET) x STRIPS	PRODUCT NAME	PROPOSED TABLETS YEAR 2010	FORECAST 2010 (kg)	TABLETS PER BATCH 2010	BATCH SIZE 2010 (kg)	NUMBER OF MIXES PER BATCH	TABLETS PER STRIP	TABLETS PER CARTON	BATCHES PER YEAR 2010	TABLETS PER STRIP X STRIPS PER CARTON	FORECAST 2005 CARTON
		PRODUCT / STRENGTH		CALC.			CALC.			CALC.		CALC.
	(2x6)x2	Product A	3,500,000	87,500	10,000	250.00	3	12	48	350	(2x6)x2	72,917
	(2x3)x2	Product B	300,000	7,500	10,000	250.00	3	6	48	30	(2x3)x2	6,250
	(2x3)x2	Product C	90,000	2,250	10,000	250.00	3	6	96	9	(2x3)x2	938
	(2x6)x2	Product D	4,050,000	101,250	10,000	250.00	3	12	96	405	(2x6)x2	42,188
			7,940,000	198,500						794		122,292

Proposed Capacity (tablets/kg) for the year

Batch Information

Packaging Configurations

Figure 3. Forecast Production Capacity Matrix which breaks down capacity in terms of tablets, kg, batches, and cartons based on predicted demand for 2010. This is based on a similar matrix (Actual Production capacity) derived from existing capacity data.

Client Product			GRANULATION													
			SCHEDULE				PER BATCH					PER YEAR				
SKU	(TABLET x TABLET) x STRIPS	PRODUCT NAME	DAYS PER YEAR	SHIFTS PER DAY	HOURS PER SHIFT	TOTAL PROCESS TIME AVAILABLE (HRS)	CYCLE TIME PER MIX (MIN)	NUMBER OF MIXES	CYCLE TIME (MIN)	CLEANING AND SET-UP TIME (MIN)	TOTAL PROCESS TIME (MIN)	TOTAL CYCLE TIME (HRS)	TOTAL CLEANNIG AND SET-UP TIME (HRS)	PROCESS EQUIPMENT UTILIZATION (%)	TOTAL PROCESS TIME REQUIRED (HRS)	NUMBER OF MANUFACTURING CELLS
		PRODUCT / STRENGTH				CALC.			CALC.		CALC.	CALC.	CALC.		CALC.	CALC.
	(2x6)x2	Product A	260	3	8.00	6,240.00	75	2	150	165.00	315	875.00	962.50	70	2,212.50	0.35
	(2x3)x2	Product B	260	3	8.00	6,240.00	75	2	150	165.00	315	75.00	82.50	70	189.64	0.03
	(2x3)x2	Product C	260	3	8.00	6,240.00	75	2	150	165.00	315	22.50	24.75	70	56.89	0.01
	(2x6)x2	Product D	260	3	8.00	6,240.00	75	2	150	165.00	315	1,012.50	1,113.75	70	2,560.18	0.41
															5019	0.80

Note: This is a sample of the GAP(I) matrix and are not actual figures.

Working Schedule

Cycle Time

No. of Mixes per Batch

Cleaning and Set-up Time

Process Equipment Utilization

No. of Process Hours

% of Process Line used. If this figure is greater than 1.0, then the process is not capable of producing the output required.

Figure 4. Typical GAP(I) analysis matrix, detailing the Granulation step.

forms for another US-based multi-nation client in Latin America. The fourth is a tripling of the capacity for a US-based firm among some of the examples.

An illustration of the process and data collection and analysis is laid-out in the flow diagram depicted in Figure 1. This data collection and analysis will be described further in detail with the article.

For the purpose of cycle time analysis, operating and theoretical data information is compiled in a matrix to represent production capacity. This is applied to the process line for a group of products. This matrix is then duplicated and modified to indicate forecast production requirements. The data in the GAP(I) analysis matrix (Figure 4) shows each operation in the process line individually and the GAP(II) analysis matrix (Figure 5) combines this information to illustrate how the process line operates as a unit.

The process will be presented further in details on how this process is applied and a case study involving a typical tablet production facility is herein included.

Capacity Enhancement Tool: The Details

A breakdown of the steps required to implement the capacity enhancement tool and of the data that needs to be accumulated is included.

Establish a Baseline

The initial part of this process is to follow the flow of material along the process line. This includes preparing "as-built" drawings of the area and material flow diagrams. The "as-built" and the line "as-it operates" will form the base line for the study and use marketing future forecast and equipment theoretical parameters to establish the needed change.

Gather Information

It is essential that detailed and accurate data is obtained so that a comprehensive analysis can be carried out. Communication with all members of the production team is vital in order to establish what is actually happening during production. Information can be gathered in a number of different manners, including questionnaires, meetings, and existing data.

Once the initial data has been compiled from separate sources, it will be collated and presented to the operating team for verification before analysis proceeds.

The required data can be split into a number of categories. The main categories are detailed below, but these may vary depending on the individual process line. This information is required for all of the products, product strength, and packaging permutations that are manufactured on the line.

Actual and Forecast Output

The current output of the process line and the forecasted requirements are essential for each product, product strength, and packaging permutation. Historical, continuously-recorded data from the operation stripped of any modifications or interpretation is the ideal.

Batch Size

The batch size of each product and product strength is required, as well as how the batch is compiled and controlled.

Number of Sub-Batches

Some of the equipment may be sized for loads that are smaller than the batch size; in this case, the batch is divided into sub batches. The number of sub-batches (or lots) per batch is required.

Tablet Size, Weight, and Shape

Tablet size, weight, and shape determine the number of tablets produced per batch and the how much waste is generated.

Packaging Configurations

The number of blisters (or strips or bottles) per carton and the number of tablets per blister/strip/bottle affects the speed of the packaging line. The packaging section will operate at different speeds for different packaging configurations. Therefore, it is necessary to know how each product is packaged.

The Working Schedule

Determining the normal working hours of the plant and the shifts worked allows the theoretical process hours available

Client Products			Central Weigh	Sifting	Granulation	Fluid Bed Drying	Dry Milling	Blending	Compression	Strip Packing and Inspection	Cutter	Stacker	Cartoning
SKU	(TABLET x TABLET) x STRIPS	PRODUCT NAME	NUMBER OF MANUFACTURING CELLS	NUMBER OF MANUFACTURING CELLS	NUMBER OF MANUFACTURING CELLS	NUMBER OF MANUFACTURING CELLS	NUMBER OF MANUFACTURING CELLS	NUMBER OF MANUFACTURING CELLS	NUMBER OF MANUFACTURING CELLS	NUMBER OF MANUFACTURING CELLS	NUMBER OF MANUFACTURING CELLS	NUMBER OF MANUFACTURING CELLS	NUMBER OF MANUFACTURING CELLS
		PRODUCT / STRENGTH	CALC.	CALC.	CALC.	CALC.	CALC.	CALC.	CALC.	CALC.	CALC.	CALC.	CALC.
	(2x6)x2	Product A	0.05	0.28	0.35	0.16	0.17	0.29	0.54	0.35	0.32	0.32	0.54
	(2x3)x2	Product B	0.04	0.07	0.03	0.06	0.07	0.02	0.11	0.08	0.07	0.11	0.13
	(2x3)x2	Product C	0.01	0.02	0.01	0.01	0.01	0.02	0.03	0.03	0.03	0.03	0.02
	(2x6)x2	Product D	0.16	0.35	0.41	0.22	0.26	0.32	0.62	0.50	0.47	0.32	0.43
			0.26	0.72	0.80	0.45	0.51	0.65	1.30	0.96	0.89	0.78	1.12

Pinch Points (> 1.0)

Figure 5. The GAP(II) analysis matrix for the entire process line summarizing the GAP(I) analysis results for each unit operation.

for each unit operation to be calculated.

Set-Up Time for Each Unit Operation

The time required to set up equipment decreases the available process hours and needs to be incorporated into the analysis.

Wait Time for Each Unit Operation

Process lines are not always designed to allow for the continuous movement of batches along the line. Occasionally, it is necessary for a batch to wait until the equipment for the next step in the line is available. This time reduces the available process time of the equipment and the output of the machine.

Cycle Time for Each Unit Operation

This is the actual time required for the batch to complete its cycle in the machine.

Cleaning Time for Each Unit Operation

Equipment cleaning time is product and equipment specific. The cleaning time per batch must be calculated. Cleaning is part of production and increases the downtime of the equipment, thereby reducing the available process hours.

Process Equipment Utilization for Each Unit Operation

Equipment items are not available for production 100% of the time due to downtime and maintenance. The process equipment utilization is shown as a percentage of the total available time for production. This percentage also may or may not include the set-up time and cleaning/comprehensive cleaning time in situations where the data available for the process does not specifically break out the set-up and cleaning hours.

Waste

All production lines produce a certain amount of waste product, either product lost during the production (formulation compounding, etc.) during product transfer or product that does not meet the required standards. The capacity figures are adjusted to incorporate this waste product.

Data Analysis

Once all the production data described above has been collected for each product, product strength, and packaging permutation, it is combined together into an Actual Production Capacity Matrix. This matrix is then duplicated and modified to reflect the forecast capacity requirements in the Forecast Production Capacity Matrix. These matrices offer the actual and forecast annual capacities in terms of number of tablets, weight, number of batches, and number of cartons.

A GAP(I) matrix is then compiled for each unit operation, for each product, product strength, and packaging permutation. The results in a single figure, represent the actual (and forecasted) production for the totality of different product permutations in a given equipment unit as a fraction of maximum theoretical capacity. For forecast calculations, this figure should not exceed 1.0 (or 100%) if forecast requirements are to be met with the existing process line.

Finally, the information from each individual GAP(I) matrix is used to create a GAP(II) matrix which summarizes the GAP(I) information for the process line as a whole and allows pinch points to be identified for both actual and forecast product figures.

Capacity Improvement Options

If the GAP(II) matrix for the forecast figures indicates that the theoretical maximum capacity requirements will be exceeded for one or more equipment items, then different options for modifying the existing process line will need to be considered. As-built drawings are used to gauge the feasibility of these options and the family of matrices already created is used to quantify the benefits of each option. The options might include the following:

- scheduling and procedural changes to optimize capacity of an existing unit
- modifications to an existing equipment item to increase capacity
- replacement of an existing equipment item with a new unit of higher capacity

- introduction of a new process line(s) in parallel to the existing process line(s)

Capacity Enhancement: A Typical Case Study

A complete oral solid dosage process line, from dispensing of raw materials to packaging, has recently been analyzed for a confidential client by using this method.

Once the analysis was complete, it became apparent from the GAP(II) matrix that under normal operation, the line would not meet the forecast demand. After scheduling changes were introduced, the line was capable of meeting demand on all but two units. The GAP(II) matrix highlighted that the Tablet Press and the Cartoner would not meet the future demand of the plant - *Figure 5*.

The analysis was completed as follows: the Actual Production Capacity matrix was assembled first and this formed the base line for the study. The matrix was then revised in accordance with the figures based on predicted demand for 2010 to generate the Forecast Production Capacity matrix - *Figure 3*. This information, in combination with equipment specific data, allowed the compilation of the GAP(I) matrices. A typical example is shown for Granulation - *Figure 4*. Using the GAP(I) matrix results for each of the unit operations, a GAP(II) summary matrix could be created which identified pinch points for the process line as a whole. Once this was completed, it became clear that the tablet press and cartoner were the bottleneck unit operations - *Figure 5*.

A number of options were presented to the client and a way forward was agreed upon as outlined below to ensure that the forecast requirements were met with minimum disruption to the existing process.

Tablet Press

It was concluded from the analysis that the existing Tablet Press would not meet the forecast output of the plant. It was decided that the most efficient solution to this problem was to replace the press with a new one. Some of the issues that were encountered during the design were the following:

- large diameter tablet
- setting up of trials to produce this large tablet
- replicating the conditions that exist on site during the trials – humidity, angle of off-loading arm, and feeding of product to the tablet press
- time scale of the project

Cartoner

The Cartoner also was found to restrict the capacity of the line as a whole. Various options, including modification of the existing cartoner and introducing a second cartoner into the line, were offered as options.

For alternative options under review, it is possible to recalculate the matrices to allow an easy cost and space comparison for those options that eliminate the pinch points. This work was completed for the options under review, which resulted in a saving of approximately 90% in both capital costs and space required between the final option chosen and the original option of installing a second production line.

Conclusion

The process of the S^4 rendered that we could have six options that each in its own way will increase the manufacturing capability of the products in question under this project to meet the future demand; meet the marketing forecast with few additional percentages as buffer. The summary of the options are as follows: go forward with the proposal as stated and go with the project as originally proposed for (\$90 million* £50 million); improve the existing operations throughput at the pinch point with different type of medications to enhance the operation which the cost ranged between (\$5.4 million*/£3 million to \$18 million*/£10 million). Additional costs on upper end options may be attributed to improvements made on the manual packing operation of the line.

*Used \$1.80 exchange rate. Project year: 2004.

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About the Author

Robert F. Dream is Director Pharmaceutical/Biotechnology for CH2M HILL Lockwood Greene. He has 24 years of industrial experience, which include cell culture, microbial fermentation, DSP, master planning, design, regulatory compliance (FDA and EMEA), cycle-time analysis, process scale-up, process yield and optimization, and management of company assets. His work has been published in numerous industry textbooks and technical journals, and he has participated in seminars and technical conferences for ISPE, Pennsylvania Biotech Association (PBA), Interphex, Interphex*California*, AIChE, ASME, and has lectured at universities. He is a registered professional engineer and is an active member of ISPE. He is a graduate from Illinois Institute of Technology (BS and MS) and Drexel University (PhD).

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Tumor-Targeted Immuno-Liposomes for Delivery of Therapeutics and Diagnostics

by Tamer A. Elbayoumi and Vladimir P. Torchilin

This article presents the findings of a report that demonstrates the potential for immuno-liposomes as tumor-targeted vehicles.

Introduction

The main goal in treating a patient with a drug is to maximize the potential of producing a therapeutic response while minimizing the unacceptable toxicity. The main problems currently associated with systemic drug administration are: even biodistribution of pharmaceuticals throughout the body, the lack of drug specific affinity toward a pathological site, the necessity of a large total dose of drug to achieve high local concentration, and most importantly, non-specific toxicity and other adverse side-effects due to high drug doses. Drug targeting, i.e., predominant drug accumulation in the target zone independent of the method and route of drug administration, may resolve many of these problems. Currently, the principal schemes of drug targeting rely on the application of nanocarriers to deliver the drug into the affected zone. The most successful targeting strategies involve physical targeting (based on abnormal pH value and/or temperature in the pathological zone), passive drug targeting (spontaneous drug accumulation in the areas with leaky vasculature via the Enhanced Permeability and Retention-EPR-effect), and/or targeting using specific "vector" molecules (ligands having an increased affinity toward the area of interest).[1]

Liposomes are nano-vesicles formed by concentric spherical phospholipid bilayers that encapsulate an aqueous space. These particles are completely biocompatible, biologically in-

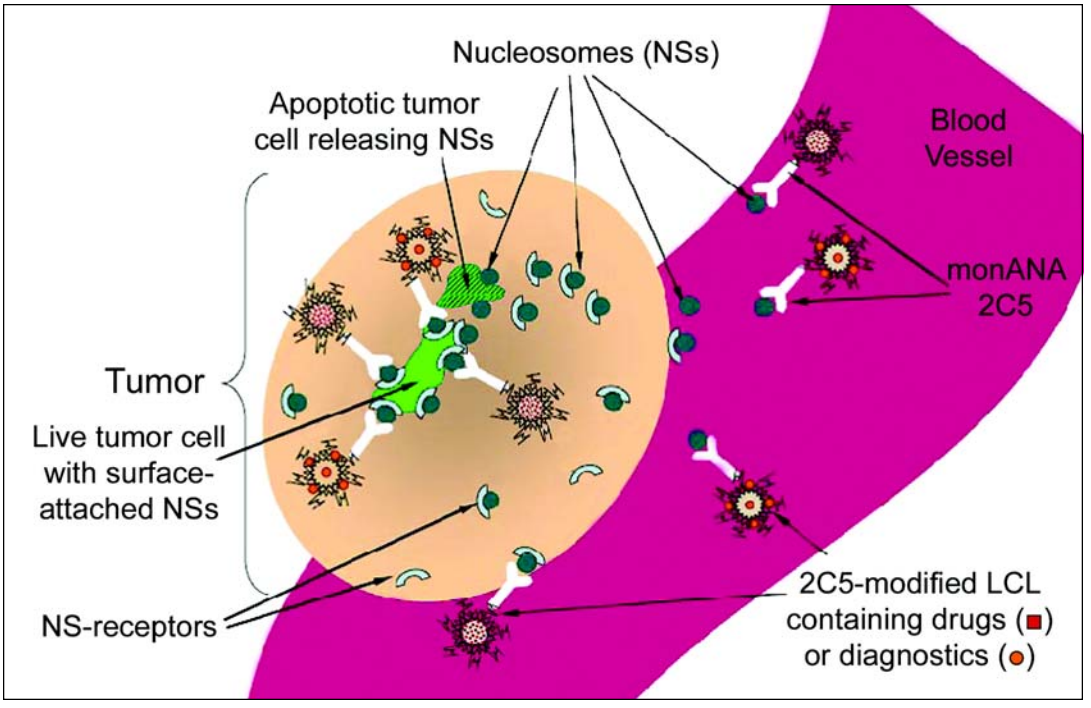

Figure 1. Tumor targeting via nucleosome-specific monoclonal antibody 2C5-modified long-circulating liposomes.

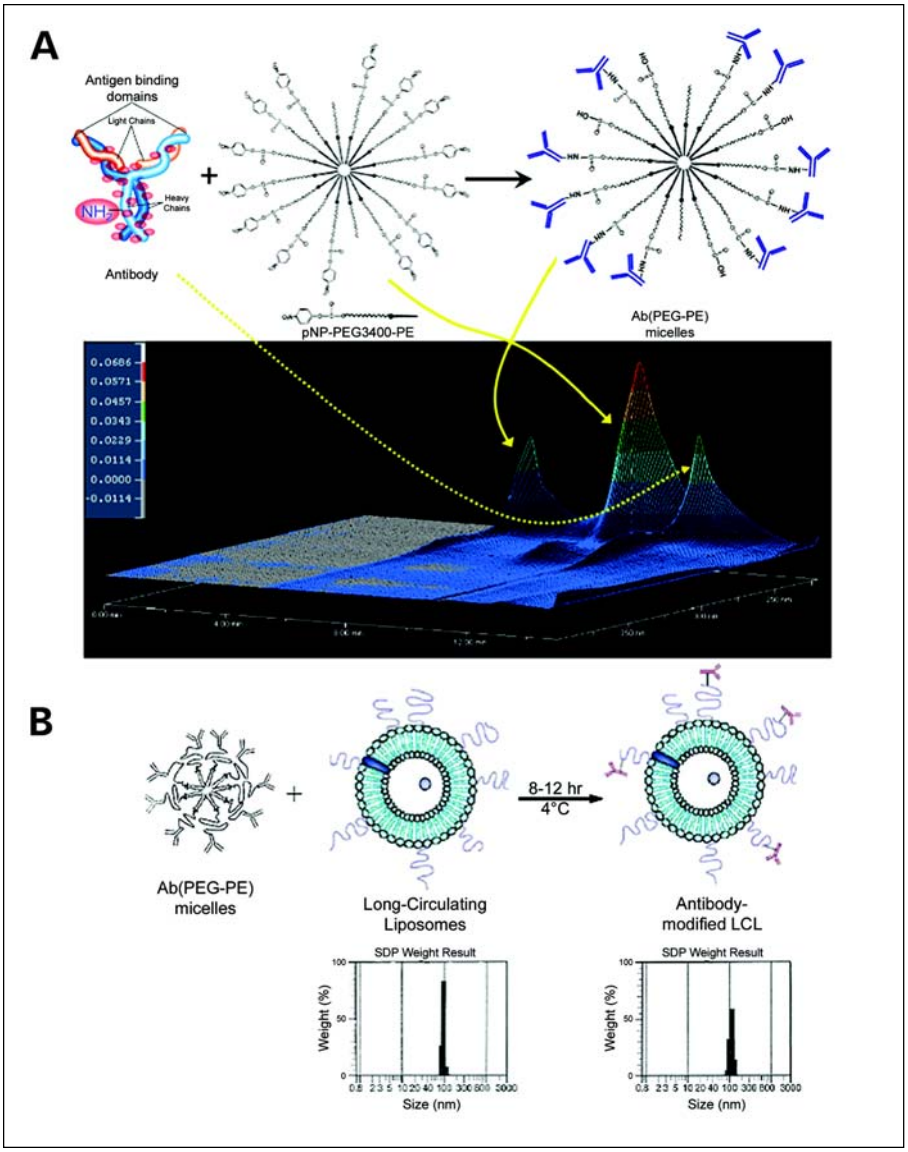

Figure 2. Schematics of antibody conjugation reaction with pNP-PEG-PE (A) showing the HPLC profile for mAb 2C5 conjugation with 40-molar excess of pNP-PEG-PE, after 24 hours (A), and the immuno-modification of Doxil® using the post-insertion method showing size measurement for both plain LCL and for LCL modified with antibody.

ert, and cause very little toxic or antigenic reactions. For drug delivery purposes, various water-soluble drugs can be entrapped in the liposomal inner aqueous space and hydrophobic drugs can be incorporated into liposomal membrane.[1] Liposomes of first generations suffered from rapid elimination from the systemic circulation mostly due to uptake by the cells of the Reticulo-Endothelial System (RES).[1] Coating of the liposomal surface with water-soluble, flexible polymer, commonly Poly Ethylene Glycol (PEG), prevented liposomes from the interaction with opsonins in the blood, which retarded their uptake by the RES.[2] These PEGylated liposomes offered not only increased circulation time,[3] but also were small enough (100 to 200 nm) so they can extravasate during their passage through the highly permeable vasculature of tumors, thus enabling their substantial accumulation in the interstitial fluid at the tumor site, a phenomenon known as EPR effect. Additionally, this PEGylated liposome technology decreased the accumulation of their cargos in non-targeted tissues.[4]

Development of Long-Circulating Liposomes (LCL) allowed for creation of Doxil® - commercial formulation of doxorubicin, incorporated into long-circulating PEG-coated liposomes, which demonstrates superior efficiency in tumor therapy and diminished adverse effects. Doxil® is currently approved for the treatment of AIDS-related Kaposi's sarcoma and ovarian cancer.[5]

Moreover, the use of liposomes in general and the PEGylated type in particular have been successfully employed as carriers for diagnostic moieties used with all the imaging modalities: gamma(g)-scintigraphy, Magnetic Resonance Imaging (MRI), and Computed Tomography (CT).[6] Owing to their unique ability to entrap different label metals, via the water-soluble chelator, DTPA,[7] or the membranotropic amphiphilic chelate, DTPA-PE.[8] LCLs were shown to accumulate sufficient amount of reporter agents into the area of interest, generating the appropriate intensity of signal to differentiate this area from surrounding tissue. The use of these passively targeted LCL as carriers for contrast agents is currently a major area of cancer research and clinical trial data on ^{111}In-labeled LCL are impressive for the detection of lung cancer,[9] skin cancer, and other malignancies.[10]

Several attempts were made to further improve the delivery efficiency of LCL by actively targeting it with vector molecules specific to receptors typical for cancer cells. Most of these vector molecules being investigated now are specific to certain types of tumors. Unlike these molecules, certain monoclonal Antinuclear Autoantibodies (ANAs) with nucleosome-restricted specificity possess an ability to recognize a broad variety of tumors. The monoclonal non-pathogenic ANAs, 2C5, and 1G3 derived from healthy aged BALB/C mice, for example, can recognize the surface of numerous tumors, but not normal cells. Apparently, tumor cell surface-bound nucleosomes (intact fragments of nuclear material, NSs) originating from apoptotically dying neighboring tumor are the targets of these antibodies on the surface of the variety of tumor cells - *Figure 1*.[11] The NS's release by dying tumor cells was hypothesized as a self-defense mechanism to protect the surviving tumor from host immune attack.[12] Hence, the subsequent increased bodily production of anti-NS cytotoxic

antibodies, like mAb 2C5, is considered a response to repress this tumor self-defense.[13]

Our report describes utilizing the mAb 2C5 as a targeting ligand to actively target long-circulating liposomes, either encapsulating chemotherapeutic agents, like doxorubicin, or incorporating ^{111}In-radioimaging moeity in their membrane, toward diverse cancer models, *in vitro* and *in vivo*. We have developed a simple and efficient way to attach mAb 2C5 to the liposomal membrane without compromising its specific activity or significantly affecting the amount or the stability of the encapsulated drug.[14] Earlier, a convenient procedure[15] for the attachment of amino group-containing ligands to the liposome surface using the lipid-conjugated PEG with its distal terminus activated with p-nitrophenylcarbonyl group (pNP) was reported - *Figure 2, Panel A*. In the original design, the activated PEG-PE (pNP-PEG-PE) was first incorporated into liposomes, which then were reacted with ligands of interest.[15,16] In our current work, an alternative design was used, where a protein was first modified with an activated lipid derivative and then incorporated into liposomes by co-incubating the micelles of PEG3400-PE-modified proteins with drug-loaded or radio-labeled liposomes - *Figure 2, Panel B*. An advantage of this approach is that the preparation of liposomes and the modification of proteins are performed separately, allowing the choice of optimal conditions for each step.[14] This "post-insertion" technique was earlier shown to provide a quantitative and stable association of antibodies and other proteins, peptides, and polymers with liposomes.[14,17] Furthermore, the simplicity of this method offers the great opportunity for easy, reproducible, and controllable industrial production scale-up, as well as unlimited tailoring possibilities using various targeting ligands and liposomal formulations.[17]

In this report, we also examined the anti-cancer efficiency of the developed targeted liposomal doxorubicin and recognition of various cancer cell lines along with the preferential localization ability of the ^{111}In-radiolabeled mAb 2C5-targeted formulation in cancer-bearing mice for adequate visualization of tumors.

Experimental Methods

Preparation of Immunoliposomes

To prepare antibody (mAb 2C5 or non-specific IgG) conjugates with PEG3400-PE, 40 molar excess of pNP-PEG-PE dispersed in 10 mg/ml micellar solution of octyl glucoside in 5 mM Na-citrate, 150 mM NaCl, pH 5.5, was added to an equal volume of 6.7mM of protein (mAb 2C5 or IgG) in Tris-buffered saline (TBS), pH 8.5. The mixtures were incubated for 24 hr at pH 8.3 at 4°C.[14]

To obtain doxorubicin-loaded liposomes modified with mAb 2C5 or non-specific IgG, proteins conjugated with PEG3400-PE [IgG(PEG-PE)$_{30}$ or 2C5(PEG-PE)$_{32}$] were mixed in equal volumes with Doxil® or LCL (composed of HSPC:CHOL:MPEG2000-DSPE in 3:2:0.3 molar ratio). Then, the remaining octyl glucoside and free, non-incorporated mAb 2C5 were removed by dialysis (250,000 Da. cutoff size).[14]

Physical Characterization of Liposomes Evaluation of Liposomal Doxorubicin Content and Release

The retention of doxorubicin by liposomes during and after the incorporation of PEG-PE-modified mAb 2C5 was estimated by doxorubicin fluorescence in dialyzed Ab(PEG-PE)$_{30}$/liposome mixtures, where samples were lysed with 0.3 N HCl in 50% ethanol and the fluorescence of obtained solutions was determined with Hitachi F-2000 fluorescence spectrophotometer at excitation wavelength of 475 nm and emission wavelength of 580 nm.[14]

The *in vitro* release of doxorubicin from the different Doxil® formulations was conducted in DMEM cell culture medium containing 10% Fetal Bovine Serum (FBS). Liposomes at a concentration of 0.5 mg/ml of doxorubicin, diluted in the media, were sealed into dialysis tubes with cutoff size of 12,000 to 14,000 Da. Then, the liposomes-loaded dialysis tubes were incubated into 50 ml of the media for 48 hours at 37°C with continuous stirring at medium speed. At various time points, aliquots were withdrawn, and replaced with equal volume of the media. The doxorubicine concentrations were then measured at 485 nm using a Hitachi U-1500 spectrophotometer.[18]

Characterization of the In Vitro Behavior of Liposomal Formulations FACS Analysis

Cells of each type – murine colon carcinoma (C26), Lewis Lung Carcinoma (LLC), and human breast carcinoma (MCF-7) – were grown in 25 ml cell culture flasks until they reached a confluence of 70%. The cells were detached by the repetitive pipetting, and then washed twice with 1% bovine serum albumin in PBS, pH 7.4. Liposomes labeled with 0.5 wt % of fluorescein conjugated with phosphatidylethanolamine (FITC-PE, Avanti Polar Lipids; total lipid concentration was in the range between 0-8 mg/ml) were added to the washed cells, and the samples were incubated for 30 min at 4°C, in 5% CO_2. After the incubation, the cells were washed twice with PBS, live-gated using forward vs. side scatter to exclude debris and dead cells and analyzed (10,000 cells in average count).[14]

Confocal Fluorescence Microscopy

After an initial passage in tissue culture flasks, murine colon carcinoma (C26), and human breast cancer (BT20) cells were grown in 6-well tissue culture plates. After reaching 70-80% confluence, the plates were washed with Hank's balanced buffer, pH 7.4, then treated with 1% BSA in 2 ml/well DMEM and incubated for 1h at 37°C, 5% CO_2. To these cells, mAb 2C5-modified Doxil® (total lipid concentration of 1 mg/ml) was added and cells were incubated for both 1h at 37°C, in 5% CO_2. After the incubation, cells were washed with Hank's balanced buffer and stained with DAPI nuclear stain (20 µl, 100 µM) for 10 min, after fixation in neutral buffered formaline (NBF) for 30 min. Following this, individual cover slips were mounted cell-side down on glass slides using fluorescence-free glycerol based mounting medium and cells were viewed with a an inverted Zeiss confocal laser scanning microscope.

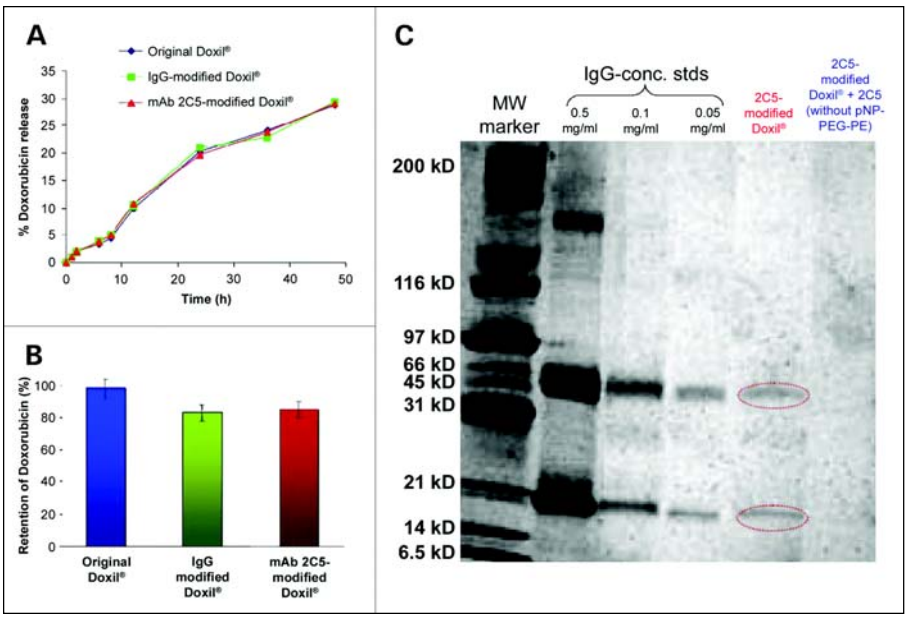

Figure 3. Characterization of mAb 2C5-modifed Doxil®. Release profile of doxorubicin from different formulations in serum-containing culture medium (A); Doxorubicin retention after immuno-modification of Doxil®(B); and SDS-PAGE analysis of mAb 2C5-modifed Doxil® for the estimation of amount of liposomes-bound antibody (C).

Cytotoxicity Assay

The cytotoxicity of various preparations of the liposomal doxorubicin against LLC, C26, BT20 and MCF-7 cells was studied using a MTS test after 24 hour incubation of liposomes with doxorubicin concentration of up to 200 µg/ml or equivalent concentrations of lipid and/or protein components, dispersed in Hank's buffer with cells grown in 96-well plates. A ready-for-use CellTiter 96® Aqueous One solution was used according to the manufacturer protocol. The cell survival rate was estimated by measuring the color intensity of the degradation product at 492 nm using a plate reader. Assay was performed twice for each cell line.[14]

In Vivo Tumor Accumulation of ^{111}In-labeled Liposomes and Gamma Imaging in Mice Tumor Models

Approximately 10^5 cells of 4T1 and LLC tumors were S.C. implanted in 8-week old BALB/C and C57/BL mice respectively, when the tumor diameter reached five to eight mm, mice were injected with 0.1 ml of 4 mg/ml ^{111}In-radiolabeled LCL formulations via the lateral tail vein. At two to 48 hours post-injections, blood was collected using a Pasteur pipette from the retro-orbital plexus of the eye, and then, the mice were euthanized by cervical dislocation followed by excision of the tumor and surrounding muscle. The amount of radioactivity was quantified as CPM using a gamma-counter. The amount of the accumulated radioactivity per gram of tissue and tumor-to-normal ratios were calculated.[15] For γ-radioimaging, mice were injected with 55µci of the respective ^{111}In-radiolabeled LCL formulations via the lateral tail vein and at different time intervals post injection, imaging was performed using a radio-isotope camera equipped with high energy collimator and NnMAC computer.

Results and Discussion

Preparation and Characterization of Liposomal Formulations

In order to combine the unique properties of long circulating and mAb 2c5-targeted liposomes in one preparation, we have adopted the "post-insertion" technique that was shown earlier[14] to provide a quantitative and stable association of antibodies and other proteins, peptides, and polymers with liposomes - *Figure 2*. The MW of PEG derivative used in our experiments to modify antibodies (PEG3400) was chosen to be higher than the MW of PEG in the composition of original Doxil® (PEG2000) to prevent possible "protective" effect of the liposomal PEG coating onto the liposome-incorporated antibody. The reaction yield (in terms of the number of PEG3400-PE groups coupled to a single protein molecule) was estimated by the loss of primary amino groups by antibody molecules due to formation of the urethane (carbamate) bonds between PEG-PE and mAb 2C5. At all polymer/protein ratios studied, the reaction yield varied between 75% and 90%, possibly depending on the accessibility to the available free amino groups on the protein molecule - *Figure 2, Panel A*.

The preservation of the specific activity of PEG-PE-modified mAb 2C5 samples was studied by ELISA using nucleosomes as a binding substrate and showed that the introduction of up to 32 PEG-PE residues per single mAb 2C5 molecule did not impair the antibody-target specific binding. Any loss in the specific activity of an individual antibody was demonstrated to be easily compensated after the attachment of multiple antibody molecules to the liposome because of a multi-point interaction between immuno-liposomes and their targets.[14] After successful conjugation of mAb 2C5 with the activated polymeric linker PEG_{3400}-PE, the 2C5 $(PEG\text{-}PE)_{32}$ conjugate incorporated successfully into the liposomal membrane through the PE anchor without inducing a significant loss of encapsulated doxorubicin or changing the release profile of the original Doxil® formulation - *Figure 3*. Moreover, the integrity of the PEG-coat of the liposomes and the surface sharge of the liposomes did not virtually change after the immuno-coupling of the antibodies (IgG/mAb 2C5). On the other hand, the size of the immuno-liposomes (Figure 2, Panel B) was 10-15 nm larger than original Doxil®, due to the presence of antibody-molecules, attached via longer PEG-linker to the liposomal membrane. The net amount of the liposome-attached antibody was determined by using the fluorescently-labeled mAb 2C5 as well as using SDS-PAGE - *Figure 3*. It was found that 55-to-60 µg of the antibody was bound per µM of HSPC, which corresponds to

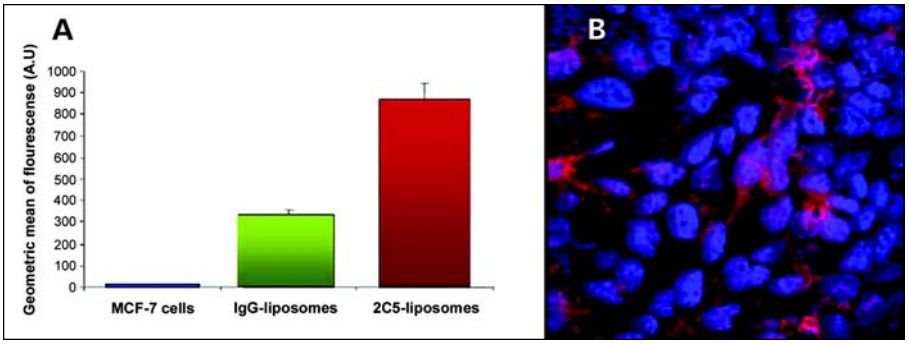

Figure 4. Flow cytometry analysis of the surface binding of mAb 2C5-targeted and control liposomes, labeled with FITC-PE, in human breast carcinoma cells, MCF-7(A); and three-D Confocal fluorescence microscopy of murine colon carcinoma C26 cells (B) incubated with mAb2C5-modified Doxil® formulation for one hour. Red color represents doxorubicin distribution and blue color represents nuclei of cells stained with DAPI stain.

approximately 80 antibody molecules per single 100 nm liposome.

In addition, unlike control nonspecific IgG-liposomes, liposomes modified with 2C5-PEG-PE demonstrated significant binding to nucleosome monolayer in ELISA test, which confirmed the preservation of specific activity by the liposome-bound mAb 2C5 (data not shown).

In Vitro Activity of Immuno-Liposomes

The ability of mAb 2C5-modified liposomes to selectively recognize target cancer cells was confirmed using both fluorescence microscopy and flow cytometry analysis (FACS) - *Figure 4, Panel A*. In all studied cell lines, both fluorescently-labeled 2C5-liposomes and 2C5-Doxil®, displayed significantly higher cancer cell binding at 4°C and cellular uptake at 37°C respectively than analogous non-targeted IgG-formulations. The confocal microscopy images Figure 4, Panel B taken after 1 hour incubation at 37°C with mAb2C5-Doxil® demonstrated a lucid and outstanding internalization of liposomal doxorubicin compared to the IgG-modified or original Doxil® controls. These findings indeed support the cell-internalization scheme conceived for these specifically targeted liposomes

Moreover, the *in vitro* cytotoxicity profile of 2C5-modified Doxil® was significantly, five to eight times, stronger than that of even the most toxic control formulation, non-specific IgG-Doxil®. At doxorubicin concentration of 50 g/ml, the mAb 2C5-targeted Doxil® formulations killed approximately 75% to 85% of cells compared to 30% to 35% of cells in case of IgG-analogue. At the same doxorubicin concentration, the original Doxil® did not kill more than 25% of cancer cells.

In Vivo Tumor Accumulation and Visualization Using Immuno-Liposomes

Using different murine *in vivo* models, the biodistribution data demonstrated that tumor accumulation ratios of ^{111}In radiolabeled 2C5-modified LCL (by addition of 0.5 M% of amphiphilic chelate, DTPA-PE to lipid composition), compared to the neighboring muscle were almost double that of the non-targeted formulations starting almost six hours post-injection (Figure 5, Panel A) despite the somewhat shorter plasma half lives of the immuno-liposomes (approximately 12 hours) compared to the native/plain LCL preparation (approximately 17 hours). The presence of the whole antibody (IgG/mAb 2C5) on the liposomal surface made more prone for RES uptake, i.e., higher clearance by liver and spleen, leading to accelerated clearance of the immuno-liposomes. Moreover, the whole-body direct gamma-imaging of tumor-bearing mice shown at six hours post administration (Figure 5, Panel B) confirms the preferential distribution of the 2C5-modified ^{111}In-labeled LCL compared to control radio-formulations towards both 4T1 and LLC tumors and demonstrate the enhanced tumor visualization in all studied models.

Conclusions

The successful modification of doxorubicin-loaded long-circulating liposomes with the anticancer monoclonal 2C5 antibody, which specifically recognizes various tumors via the tumor cell surface-bound nucleosomes, proves further enhancement in the cytotoxicity and the *in vivo* targetability of the formulation. The application of this novel targeted liposomal platform of doxorubicin provides a promising potential for an effective treatment as well as visualization of diverse tumors.

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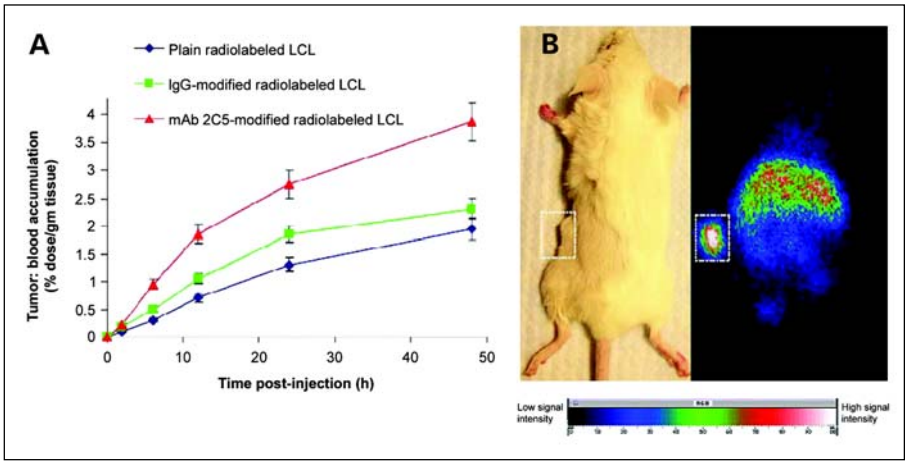

Figure 5. In vivo tumor accumulation of various ^{111}In-labeled liposomal formulations using murine Lewis lung carcimona (LLC) model (A) (n = 5, results indicated ± SD); Whole body gamma-imaging of murine breast 4T1 tumor-bearing mice, six hours after injection with 2C5-modified ^{111}In-labeled liposomes, Circles indicate tumor locations (B).

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Vladimir Torchilin, PhD, DSc is the Distinguished Professor of Pharmaceutical Sciences and Chairman of the Department of Pharmaceutical Sciences, Northeastern University, Boston since 1998. He earned his MS, PhD, and DSc from the Moscow State University and in 1991, he joined Harvard Medical School as the Head of the Chemistry Program, Center for Imaging and Pharmaceutical Research, and Associate Professor of Radiology. He is a Review Editor for the Journal of Controlled Release and on Editorial Boards of 10 journals. Dr. Torchilin is the author of more than 300 scientific papers and 90 reviews and book chapters. He authored and edited eight books and holds more than 40 patents. In 2005, he received the AAPS Research Achievement Award in Pharmaceutics and Drug Delivery, and he is currently the President of the Controlled Release Society.

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Validation Services for Clinical Markets

Millipore has announced the availability of validation and qualification services for the Elix® Clinical water purification systems. Recently, the Clinical and Laboratory Standards Institute™ issued a new guideline for "Preparation and Testing of Reagent Water in the Clinical Laboratory" that addressed the merits and importance of validation for water purification systems. Specifically designed to meet this need, Millipore's validation service gives the user peace of mind in knowing that their system has been installed and is operating according to pre-determined specifications.

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

Digital Vacuum Ovens

SP Industries has announced the availability of their Hotpack brand Programmable Digital Vacuum Ovens which feature microprocessor controlled ramp and hold programming capability with up to eight steps for temperature as well as vacuum set points. Engineered for more demanding test applications, Hotpack Vacuum Ovens provide high temperature operating capability to 280ºC with bottom-out deep vacuum to 10 mTorr. Convenient digital setting and LCD readout enable performance parameters to be accurately set and monitored and an alarm function provides audio alert of any deviation from set points.

SP Industries, 935 Mearns Rd., Warminster, PA 18974, www.spindustries.com.

Transducer with Local Indication

The new Ashcroft® Xmitr™ combines the advantages of the proven Ashcroft® Power*Flex*™ pressure gauge with the patented transducer technology to create a single, convenient, dual-function instrument. Serving as "2 instruments in 1," the Xmitr™ provides traditional transducer features including 4-20mA and voltage outputs, CE ratings, and 1% BFSL accuracy with electronic temperature compensation from -20°C to 85°C. Pressure ranges from 30 psi to 5000 psi are available in three configurations: Type X1005 with a 2" dial and Type X2001 with a 2.5" or 3.5" dial.

Ashcroft Inc., 250 E. Main St., Stratford, CT 06614, www.ashcroft.com.

Orbital Tube Welder

Arc Machines has announced the addition of new features and system upgrades to the Model 307 Tube Welding Power Supply. New features and system upgrades include: operating system upgrade to Windows XP; RAM increase from 64 to 256 MB; sloping between levels that smoothes out "steps" seen in critical welds; slope distance programmed in actual time or degrees; and operation in 33 pre-programmed languages. Upgrades are free for existing Model 307 customers.

Arc Machines, Inc., 10500 Orbital Way, Pacoima, CA 91331, www.arcmachines.com.

Validation Support Package for TOC Monitoring

The new 5000TOC Sensor Validation Support Package from Mettler-Toledo Thornton helps achieve a fully qualified (IQ/OQ) system for total organic carbon (TOC) measurements in pharmaceutical water production systems. It guides the operator through specific procedures and facilitates compliance with regulatory audits by providing standardized protocols. The Validation Support Package supplies the tools needed to monitor operational condi-

tions for regulatory requirements and furnishes documented evidence that the instruments will produce accurate results.

Mettler-Toledo Thornton, 36 Middlesex Turnpike, Bedford, MA 01730, www.thorntoninc.com.

Process System Resource

Process System Solutions (PSS) is a new business group of Continental Disc Corporation. PSS provides single-source solutions for process system projects from concept through commissioning, qualification, and validation. The company offers engineered products along with pre- and post-sale services to the pharmaceutical, biotechnology, chemical, oil and gas, food and beverage, wastewater, and OEM industries.

Process System Solutions, 3160 W. Heartland Dr., Liberty, MO 64068, www. prosyssol.com.

Signal Conditioners

Action Instruments, a division of Eurotherm, has announced that their signal conditioners are now approved for use in hazardous area locations. The WV408 - DC voltage/current input isolating signal conditioner and the WV428 - Thermocouple input isolating signal conditioner can both be installed directly in the Class I, Div 2 [Groups A, B, C and D] hazardous locations. Significant labor savings over traditional protection methods can be enjoyed because there is no need for explosion proof enclosures and conduits.

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

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Annual Meeting to Feature FDA, Industry Leaders

ISPE officially invites you to the 2006 ISPE Annual Meeting, where pharmaceutical industry professionals will gather from around the world to address the multi-layered challenges of innovation, 5-8 November in Orlando, Florida, USA.

Moheb Nasr, Director, ONDQA, CDER, of the US FDA, will present the US FDA perspective on the need for strategic innovation in the industry. Nat Ricciardi, President of Pfizer Global Manufacturing, will offer insights and the necessities of innovations in our changing industry.

In addition, a major company will present its experience of the FDA's CMC pilot program and how they are applying science-based and risk-based approaches to the development of a new product.

The Annual Meeting is a premier opportunity to bring pharmaceutical manufacturing professionals from around the world together for interactive workshops, discussion forums, keynote sessions to explore major trends, and classroom seminars taught by leading industry experts from around the world.

Moheb Nasr
Director,
ONDQA,
CDER, FDA

Nat Ricciardi
President of
Pfizer Global
Manufacturing

Other highlights of the meeting include:

- Workshops on the new Certified Pharmaceutical Industry Professional™ (CPIP™) credential
- A forum on the 2006 Facility of the Year Finalists
- A chance for Members to join a Community of Practice to learn and socialize with like-minded professionals and network with an international roster of industry professionals
- The National Institute for Pharmaceutical Technology and Education (NIPTE) Colloquium
- Tech vendor sessions

INNOVATING CHANGE: Gert Moelgaard, ISPE Chairman, accepts the Commissioner's Special Citation from the US Food and Drug Administration (FDA)from Dr. Janet Woodcock, the FDA's Deputy Commissioner of Operations, at the Society's 2005 Annual Meeting. The presentation was made in recognition of ISPE's "outstanding commitment and many years of continued support of crucial initiatives including the drug shortage program, the Process Analytical Technology Initiative, the reform of 21 CFR Part 11, and the Risk Based Inspection Model, as well as significant contributions to preparing for training the pharmaceutical professionals of the future."

Educational sessions include:

- A Vision for the Future: Practical Applications of the proposed ASTM Standard for a Science- and Risk-based Approach to Qualification
- Drug Shortages and Industry Preparedness
- Process Development in the New Quality By Design Framework
- Biotechnology: The Industry Impact on a Global Economy
- RFID Trends, Challenges, and Solutions for Life Sciences
- Commissioning Qualification (C&Q), and Validation of Process Control Systems (VPCS): The Next Generation of GAMP
- ASTM Standards for PAT and General Pharmaceutical Manufacturing: A Status Report

Continued on page 4.

Welcome to the New World

In an effort to focus on innovation, ISPE will promote the Annual Event through its latest communication vehicle, the ISPE blog, which will allow Members – both present and those not able to attend – to post comments, insights, and information that would be helpful to other Members.

This Web log – or blog, for short — is similar to an online diary or journal on a Web site and is displayed in reverse chronological order. The Society will post information about the Annual Meeting, and Members can send in questions or comments about the Annual Meeting.

The blog will include summaries of important sessions, keynote speakers, photos of Members, and other information about the Meeting. The blog will be linked to the ISPE Web site for additional information. Members will be able to post comments on the blog at an onsite kiosk with laptop computers, or post from their own computers.

In addition to the blog, the Society will feature Innovation I-Way, a historical look at the successes of ISPE in the past 25 years, leading up to its Communities of Practice, relationships with the FDA and its new Strategic Plan which will help guide the pharmaceutical manufacturing industry in the future. PE

Join Your Community of Practice

In an industry that changes constantly, ISPE is at the forefront. ISPE understands the critical need of professionals to know the industry, particularly when it comes to tracking emerging trends.

By joining an ISPE Community of Practice (COP), Members have instant access to a network of like-minded practitioners who want to learn and work together to address regional, domestic, and global issues in their particular areas of expertise.

ISPE's Communities of Practice allow Members to target their needs by joining like-minded professionals to exchange ideas about their fields.

ISPE encourages Members with experience, knowledge, or interest in any of the disciplines represented by the various Communities to get involved. Becoming a COP Member is easy and convenient and can be done by visiting www.ispe.org/cops and clicking on the "subscribe" tab.

The purpose of ISPE COPs is to:

- Provide a forum for community Members to help each other solve everyday work problems and engage in active networking.
- Develop and disseminate best practices, guidelines, and procedures for use by community Members
- Organize, manage, and research a body of knowledge from which Community Members can draw
- Innovate and create breakthrough ideas, knowledge, and practices

The Communities of Practice include:

Active Pharmaceutical Ingredients (API)

The API COP proactively advocates the importance of API in the drug product delivery process with the objectives of providing a forum for Members to discuss issues of common interest through: education and training; E-Discussions; regulatory cooperation; information dissemination; and establishment of links to internal and external groups with common interests.

Biotechnology (BIO)

The Biotech COP aims to create a global focal point of support for pharmaceutical professionals operating in the Biotech sector. Support means the creating and delivery of training, technical materials and information, and providing opportunities for collaboration and networking.

Clinical Materials (CM)

The Clinical Materials COP provides a forum for Members to discuss issues of common interest, and when appropriate, to propose solutions to common industry problems; proactively advocate the importance of Clinical Trials Materials in the drug approval process; and support ISPE in achieving its goals.

Commissioning and Qualification (C&Q)

The C&Q COP aims to align the processes of commissioning and qualification with a science and risk-based approach, provide input and guidance into other documents, and to facilitate understanding and organizational change necessary to implement this approach. This will be accomplished through: discussion and communications forums; education and training; guidelines and standards review; and facilitating links to other groups with common interests.

Containment

The Containment COP provides a forum for all those involved in the safety of patients and people from exposure, contamination, and cross contamination of hazardous compounds and interact with all appropriate stakeholders to share, influence and change knowledge, guidance, and regulation for the good of all.

Critical Utilities (CU)

The Critical Utilities COP provides a discussion forum and network for Critical Utilities professionals by encouraging the sharing of ideas relevant to topics such as system design, commissioning & qualification, process validation, requalification, regulations, operations, and maintenance.

Good Automated Manufacturing Practice (GAMP)

The GAMP Community exists to promote the understanding of the regulation and use of automated systems within healthcare industries.

Heating, Ventilation, and Air Conditioning (HVAC)

The HVAC COP is the premier global organization that serves as a one-stop

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

Join Your COP

Continued.

shopping outlet and provides relevant, timely information and solutions to real-world problems related to HVAC for pharmaceutical facilities.

Investigational Medicinal Products (IMP)

The IMP COP provides a forum for Members to discuss issues of common interest, proposes solutions to industry problems, and facilitates interaction with regulatory bodies.

Process Analytical Technology (PAT)

The PAT COP creates a global focal point of support and a discussion forum for pharmaceutical professionals interested in Process Analytical Technology. This means the creation and delivery of training, technical materials and information, as well as providing opportunities for collaboration and networking.

Process/Product Development (PPD)

The PPD COP is a dynamic forum for professionals in product/process development to discuss and address issues of common interest.

Project Management (PM)

The Project Management COP is a dynamic forum for professionals working within the pharma industry who have an active interest in promoting "continuous improvement" project management by creating a body of knowledge specific to the professional needs of its Members.

Sterile Products Processing (SPP)

The SPP COP aims to establish and manage a forum that supports all facets of sterile products processing; enables common interest discussions; provides access to relevant information; and supports member networking.

E-Letters Gives You Information You Need

ISPE is proud of its new E-Letters, our customized electronic newsletters geared toward Communities of Practice. E-Letters address your needs as a professional in the pharmaceutical industry based on your specific areas of interest and feature industry news about best practices, regulatory news, technical articles, and innovative solutions.

In May, we released our first four E-Letters, which included newsletters on information about GAMP, Containment, Clinical Materials, and PAT. In August, continuations of those letters were sent out, with additional E-Letters on Biotechnology, C&Q, API, and PPD.

The next installment of E-Letters will be mailed electronically in November and will include PM, HVAC and CU.

We have received positive feedback about E-letters, including that it is a valuable addition for members. In particular, we heard great comments and suggestions at our Washington Conferences in early June and at our Leadership Retreat in July. Many Members were eager to get on board and contribute to another opportunity to stay connected to their area of interest.

If you are a member of a Community of Practice you will automatically receive your COP's E-Letter.

Starting in 2007, E-Letters will be on an opt-in basis, so you will need to let us know which categories you are interested in to be sure you get your E-Letter.

You can update your interests by filling out a subscription form on our Web site. You can contribute to E-Letters by sending ideas or articles to mstrickhouser@ispe.org, or rrunas@ispe.org. You can advertise in E-Letters by contacting Dave Hall at dhall@ispe.org.

You can view all E-Letters at www.ispe.org/e-letters.

New Electronic ISPEAK Sent to Membership

ISPE has changed its long-running Society newsletter, ISPEAK, to electronic format, launching the premier issue 28 July. In addition to this newsletter sent by e-mail, news is regionalized by Europe, Asia-Pacific, and North America and South America. Please be sure to click on the ISPEAK link to get the full global newsletter.

Members can access the bi-monthly newsletter on our Web site under "publications." The next electronic edition of ISPEAK will be sent 29 September.

To submit information, please e-mail Marsha Strickhouser, Public Relations Manager, at mstrickhouser@ispe.org or contact her at +1-813-960-2105, ext. 277. To purchase an advertisement, please contact Dave Hall, Director of Advertising, at dhall@ispe.org or call +1-813-970-2105, ext. 208.

Journal of Pharmaceutical Innovation Makes Debut This Month

ISPE has launched its new *Journal of Pharmaceutical Innovation (JPI),* a scientific, peer-reviewed journal for the publication of research and review articles. As a Member benefit, your copy was sent to you with this issue of Pharmaceutical Engineering.

The pilot journal was produced in partnership with Reed Elsevier, which also publishes *Cell* and *The Lancet*. Two years ago, the US FDA asked ISPE to play a prominent role in the FDA's plan to be a catalyst for change "to enable fully flexible manufacturing concepts, within regulation, using the best engineering and scientific principles available, improving business and taking risk into consideration."

In response to this challenge and with Board of Directors' support, ISPE has embarked on several initiatives in consultation with the FDA, including launching this scientific peer-reviewed journal.

ISPE is pleased to have the support of James K. Drennen III, Associate Professor, Duquesne University, Pittsburgh, PA, USA, who will serve as the Editor of *JPI*. Dr. Drennen is Head of the Pharmaceutical Sciences Division at Duquesne University in Pittsburgh, Pennsylvania. He is co-founder and Director of the Duquesne University Center for Pharmaceutical Technology, and Associate Professor of Pharmaceuticals.

In addition, he is the North American Editor for the Journal of Near-Infrared Spectroscopy and Pharmaceutical Editor of the newsletter, NIRnews. Currently, Dr. Drennen serves as the Membership Secretary of ASTM International Committee E55 on Pharmaceutical Application of Process Analytical Technology.

JPI is intended for the publication of research and review manuscripts emphasizing new and innovative methods and techniques used by pharmaceutical professionals serving all aspects of the industry including Manufacturing, Applied Pharmaceutical Science and Technology in Process, and Product Understanding and Control.

JPI will be mailed to Members along with *Pharmaceutical Engineering*. The *Journal of Pharmaceutical Innovation* will reach 23,000 ISPE Members in 81 countries. In addition to ISPE Members, *JPI* will have an additional distribution of 15,000 international industry and academic professionals. The journal will be available in print and online versions free to ISPE members.

The new journal will include the following categories of articles:

- **Perspectives** are opinion articles on controversial topics or recent developments in the industry, or can cover strategic industry issues, new areas of research, profiles of new research organizations or industry trends.

- **Case Studies** provide a critical analysis of the implementation of a new method or technology.

- **Research Letters** are short papers reporting results that are of genuinely broad interest, but that do not make a sufficiently complete story to justify publication as a full Research Article.

- **Research Articles** describe, in detail, new and innovative methods and techniques, with conclusions that are supported by adequate evidence. Scientific rigor and reproducible results are required.

- **Reviews** may address both the recent scientific advances in drug development, pharmaceutical engineering, and manufacturing, as well as the management, commercial and regulatory issues that increasingly play a part in how R&D is planned and performed.

For information or inquiries regarding editorial content, please contact Gloria Hall at ghall@ispe.org. To inquire about advertising, please contact Dave Hall at dhall@ispe.org.

Annual Meeting...

Continued from page 1.

- Energy Sustainable Design - Build Green Procurement and Contract Strategies for the Changing Pharmaceutical Industry
- GAMP Data Migration Good Practice Guidance

And special series designed for your needs will feature:
- Executive Series: The Real World of Project Management - Critical Utilities Projects and Programs
- Facilities Series: Vaccine Facilities of the Future
- Regulatory Series: Quality By Design - What the ICH Guideline Q8 Says About QBD6
- Manufacturing Technology Series: Continuous Processing in the Real World

Register on-line now and watch www.ispe.org for updates, or call ISPE at + 1-813-960-2105.

Sponsorship and exhibit opportunities are still available for the 2006 Annual Meeting. Please contact Dave Hall, ISPE Director of Sales, by tel: + 1-813-960-2105, or e-mail: dhall@ispe.org

Taking the Initiative:

ISPE Joins Forces with University to Develop Training Program for High School, College Students

ISPE has joined forces with the University of Florida, in Gainesville, Florida, USA, along with the National Science Foundation, and 40 partners in education, government, and industry, in order to train workers for Florida's growing biotechnology industry.

Recently, the NSF awarded $599,997 to the University of Florida's Center of Excellence for Regenerative Health Biotechnology (CERHB) to fund the Florida Partnership for Industrial Biotechnology Career Development and Training.

ISPE's role in this partnership will be to help develop the training program and teach community college and high school instructors the essentials of "Good Manufacturing Practices" - inspection and certification standards enforced by the US Food and Drug Administration that are observed when manufacturing and testing drugs, medical devices or other agents that come in contact with people.

"This will help students and workers get higher-paying jobs and find better careers," said Richard Snyder, director of UF's Center of Excellence for Regenerative Health Biotechnology. "Likewise, having state-of-the-art training for our workforce will stimulate the creation of high-wage, high-skill jobs in what is regarded as a clean industry. It's definitely a win-win scenario."

Snyder and Win Phillips, UF's vice president for research, said the partnership will create training programs at the CERHB's education center, at Santa Fe Community College in Gainsville, and within the Alachua and Marion County public school systems, with the expectation that these programs will eventually be reproduced throughout the state.

The partnership will begin by training instructors and developing coursework that is useful and appealing to high school and college students, as well as to workers interested in switching to entry and mid-level careers in the biotechnology industry, according to Bob Best, President and CEO of ISPE, a key collaborator in the effort. The goal is to create model curricula and programs that can be reproduced throughout the state and the nation.

Most current training programs are concentrated in existing biotechnology clusters in states such as California and Massachusetts, according to Harry Orf, vice president for scientific operations and professor of chemistry at Scripps Florida and chairman of the education and community outreach committee for BioFlorida, a statewide bioscience organization.

"Addressing the need for a better-prepared workforce improves the candidate pool for us," Orf said. "Historically, the biotechnology industry hasn't been in place here, so there hasn't been the need for the workers. If we're going to build the industry, we have to build the workforce."

Work in the biotech field requires understanding scientific principles involved in diverse areas such as DNA research, genetic analysis, protein purification, drug manufacturing, and product testing. Furthermore, workers

Continued on page 6.

ISPE Forms Partnership with North Carolina Colleges for Biotechnology Validation

ISPE has renewed its License Agreement with the North Carolina Community College System for the development of the BioNetwork Validation Service Academy.

The North Carolina Community College BioNetwork Validation Academy is a partnership between BioNetwork, ISPE, and the North Carolina Department of Commerce. The academy is a major attraction for new companies wishing to open pharmaceutical or biomanufacturing facilities in North Carolina, and for growing companies that are planning facility expansions.

"Launching the BioNetwork Validation Services Academy is an historic milestone in training pharmaceutical and biotechnology manufacturing professionals," said Bob Best President and CEO of ISPE. "ISPE is proud to partner with NCCCS by offering our training courses based on a practical applications approach to learning utilizing their pioneering training facility. This partnership is a monumental step forward by providing a bridge between academia and industry."

ISPE's role includes that of validation, the regulatory requirement for biopharmaceutical facilities, and the written proof a pharmaceutical or biomanufacturer must be able to provide to demonstrate with a high degree of assurance that a process or system will consistently produce their medicine to safe standards.

Jeff Odum, validation academy manager, is an ISPE member and chairperson of its North American Education Committee – the body that develops and executes international training programs for the biopharmaceutical industry.

Odum, who is in charge of curriculum including case studies, research, and group activities, is a nationally-recognized validation expert and author who provides industry insight in the areas of regulatory compliance, facilities and process design, and project management for biopharmaceutical companies.

ISPE Joins Forces...

Continued from page 5.

need to know regulatory and quality control procedures.

It's a unique set of skills, but once acquired, students who have them will find themselves in demand, according to Jackson Sasser, president of Santa Fe Community College.

"Students have for a few years been filling every opening in Santa Fe's Biotechnology Laboratory Technology degree program, and employers have been hiring them once they graduate," Sasser said. "This is not surprising. SFCC and the UF Biotechnology program are partners in this program, and its course content is developed with advice and direction from our partners in the biotechnology industry."

Beyond the Gainesville area, which includes UF's $500 million research enterprise, area health-care facilities and sprouting biotechnology companies, the market for skilled employees in Florida is expected to become even livelier because of Scripps Florida, a major research center planned in South Florida. Scripps is expected to employ more than 500 workers and eventually create 200 new businesses and 16,000 new jobs.

Call for Submissions for 2007 Facility of the Year Awards

ISPE, along with co-sponsors INTERPHEX and *Pharmaceutical Processing*, invites you to enter your submissions of plans of new facilities for pharmaceutical manufacturing organizations, for its global 2007 Facility of the Year Awards (FOYA) competition.

FOYA, in its third year, is an annual competition to recognize state-of-the-art pharmaceutical manufacturing projects that utilize new and innovative technologies to enhance the delivery of a quality project, as well as to reduce the cost of producing high-quality medicines. Award-winning facilities are those that demonstrate global leadership and showcase cutting-edge engineering, innovative new technology, or advanced applications of existing technology.

FOYA was instituted to recognize accomplishments, shared commitment, and dedication of individuals in companies worldwide to innovate and advance pharmaceutical manufacturing technology for the benefit of all global consumers.

"We want to give recognition to those who design, build, and operate world-class pharmaceutical manufacturing facilities," said Scott Ludlum, ISPE's Director of Business Initiatives. "And this year the Awards have expanded in order to raise awareness for these vital segments of the global pharmaceutical industry."

This year, several significant enhancements have been added to the Awards program, including six awards categories in:

- Process Innovation
- Project Execution
- Equipment/Innovation
- Facility/Integration
- Energy Management
- Operational Excellence

In addition to the new categories, winners will be recognized and introduced during INTERPHEX 2007 in New York City, where thousands of attendees convene for one of the largest industry events worldwide.

The announcement of the overall winner of the coveted Facility of the Year Awards competition will take place at ISPE's Annual Meeting in November 2007 at Caesar's Palace in Las Vegas. A Facility of the Year Awards display will feature the Category Winners and Facility of the Year Awards winner. The winner will receive the prestigious crystal and marble trophy, as well as various publicity initiatives through ISPE, *Pharmaceutical Engineering*, INTERPHEX and *Pharmaceutical Processing*. Key contributing organizations also will be included in overall publicity.

The deadline to submit applications for the 2007 competition is 8 December 2006. For complete information about the Awards program and submission procedures, as well as to download the online application form, please visit www.facilityoftheyear.org. Specific questions can be addressed to Scott Ludlum, ISPE Director of Business Initiatives, by tel: +1-813-739-2284 or by e-mail: sludlum@ispe.org

The 2006 overall FOYA winner was Baxter BioPharma Solutions. Finalists last year included AstraZeneca, Daiichi Asubio, Janssen Pharmaceutical, and Wyeth Pharmaceuticals. Special recognition went to Biolex Therapeutics. For more information on winners from 2005 and 2006, visit www.facilityoftheyear.org.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

New CPIP™ Certification Program – Seal Your Career in Gold

Recognizing the need for change within the pharmaceutical industry to im-prove drug product manufacturing processes, quality, and consumer cost effectiveness, the ISPE Professional Certification Commission™ (PCC) has announced its Certified Pharmaceutical Industry Professional™ credential — the first competency-based professional certification for pharmaceutical professionals. And it could help you seal your career in gold.

"Our industry benefits from employees certified in diverse knowledge, and from the ability to apply this knowledge across all segments of our industry," said Ali Afnan, PhD, US FDA. "In addition, it allows employers to be able to recognize top performers, attain better product quality, industry-wide recognition, and commitment to innovation. Certified employees will become more valuable as team leaders, develop keener awareness, and perform their job more efficiently."

The CPIP™ credential will recognize professionals as "change agents" to help drive industry innovation. This call for change encourages new science and risk-based approaches for drug product development, manufacturing and distribution, and is supported by government regulators. ISPE-PCC recognizes the need for change and is leading the efforts by developing and implementing this innovative certification as a means of advancement within and for the industry.

Eligibility applications will be available in November 2006, along with several workshops offered onsite at the ISPE 2006 Annual Meeting to be held 5-8 November in Orlando, Florida, USA. The first CPIP™ examination will be scheduled for July 2007.

"The certification program will help enact change in the pharmaceutical industry by recognizing professionals who facilitate innovation in development and manufacturing, thereby enhancing opportunities for drug product excellence," said Jerry Roth, PE, ISPE's Director of Professional Certification.

The CPIP™ certification has appeal and value for professionals from:

- Drug Product Development
- Drug Product Manufacturing Operations
- Facilities/Process Engineering
- Facility and Process Equipment Manufacturing/Supply
- Project Management
- Regulatory Compliance/QA/Validation
- Technical Support

The CPIP™ will have broad industry knowledge and experience and apply key competencies to achieve cost-effective, risk-based approaches, innovation, quality by design, and continuous improvement.

The professional conferred the competency-based CPIP™ credential will have demonstrated the application of competencies including technical knowledge, leadership skills, and innovative problem solving.

Employers benefit from employees' certification because it assures that employees have diverse knowledge and the ability to apply that knowledge across many segments of the industry. The CPIP™ designation also allows employers the opportunity to recognize top performers, improve product quality, operate with global competency standards for professionals, and realize industry innovation.

At the same time, pharmaceutical industry professionals benefit through increased professional advancement, enhanced credibility, peer respect and recognition, a competitive edge for job seeking, new job opportunities, and personal satisfaction.

The pricing structure for the CPIP™ credential is:

Application Fee	ISPE Member: $100 USD, EUROS €80 Nonmember: $200 USD, EUROS €160
Examination Fee	ISPE Member: $300 USD, EUROS €240 Nonmember: $400 USD, EUROS €320
Re-certification Application Fee	ISPE Member and Nonmember: $225 USD, EUROS €180

All fees are non-refundable. Recertification will be required every three years from the date the credential is conferred.

To learn more about the CPIP™ credential, and the eligibility criteria, visit www.ispe-pcc.org.

Regulatory

ISPE/PDA Conferences to Examine Guidances for Industry with ICH Think Tank

by Rochelle Runas, ISPE Technical Writer

Members of the International Conference on Harmonisation (ICH) Expert Working Groups who wrote "Q8 Pharmaceutical Development" and "Q9 Quality Risk Management" have been enlisted to develop content and give presentations for the upcoming joint ISPE/PDA Conferences.

"Challenges of Implementing Q8 and Q9 – Practical Applications," will be held 6-7 December 2006 in Washington, D.C., USA, and 12-13 February 2007 in Brussels, Belgium, and on a date to be determined in 2007 in Japan.

The conferences will be hosted by ISPE and the Parenteral Drug Association (PDA), two leading associations in the pharmaceutical manufacturing industry that have joined forces to further explore the recently published Guidances for Industry, ICH Q8 and Q9.

The FDA issued Q8 on 22 May, and just two weeks later, issued Q9. The Guidances for Industry are expected to have a major impact on how the industry and those who regulate it will do business.

Conference developers say the worthwhile event will take attendees on a backstage tour of the ICH negotiating table, looking at not only what is in the Guidances for Industry, but also at what wasn't included and why. Nearly 15 representatives of the ICH Expert Working Groups are involved in the conference planning and presentations.

Regulators and industry representatives from the US, Europe, and Japan will describe the challenges involved with the implementation and application of the Guidances for Industry in their respective regions.

Regulators from the US FDA, EU EMEA, and the Japanese Ministry of Health, Labor, and Welfare, will consider how to:

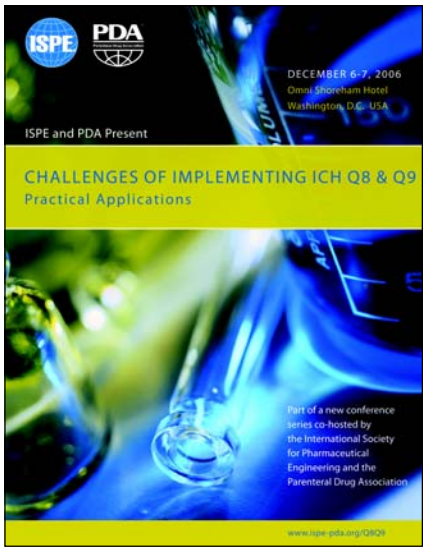
- conduct science and risk-based assessment of submissions
- balance expectations for a quality by design-based submission and approval of a product without raising the bar
- provide regulatory flexibility while still assuring product quality
- handle legacy products

Industry representatives from all three regions will provide their perspective of the challenges associated with the implementation of the Guidances for Industry, including a review of the potential benefits, such as enhanced process capability and robustness, better integration of review and inspection systems, achieving greater flexibility in specification setting, and the management of post approval changes.

In addition, through case studies, attendees will learn from regulators and industry representatives about experiences with the FDA's CMC Pilot Program, EFPIA's Pharmaceutical Development model, and the implementations of strategies for quality risk management.

Representatives from both ISPE and PDA will provide updates on their associations' work relative to Q8 and Q9. Panel discussions will provide opportunities for interaction between speakers and attendees. The conferences will be structured so that all attendees have the benefit of attending all sessions and hearing all presentations.

Registration details will be forthcoming and will soon be available for viewing at www.ispe.org and www.pda.org.



ISPE ENGINEERING PHARMACEUTICAL INNOVATION

Mark Your Calendar with these ISPE Events

October 2006

5 Argentina Affiliate, Educational Activities, "Modulo 4: Sistemas para Distribucion y Acumulacion de Aguas PW/WFI," Hotel IBIS, Buenos Aires, Argentina

5 Greater Los Angeles Area Chapter, Evening with Industry Executives, Facilities Presentation with Panel Discussion, Facility Tour of Gilead, Los Angeles Area, California, USA

5 Nordic Affiliate, GAMP Conference, "Outsourcing IT," Park Inn Copenhagen Airport Hotel, Copenhagen, Denmark

5 San Francisco/Bay Area Chapter, Commuter Conference, "Water Treatment Systems," Pipe Trades Training Center, San Jose, California, USA

9 Midwest Chapter, Educational Session and Golf Outing, Millwood Golf Course, Springfield, Missouri, USA

9 - 12 ISPE Prague Training, Crowne Plaza, Prague, Czech Republic

10 Delaware Valley Chapter, Program Meeting, USA

12 Ireland Affiliate, Seminar, "Pharmaceutical Documentation," Dublin, Ireland

12 Italy Affiliate, Seminar, "Cost Efficiency - New Technologies, Effectiveness, and Quality in Pharmaceutical Supply Chain," Grand Hotel Baglioni, Firenze, Italy

12 UK Affiliate-North West Region, Seminar, "Management of Pharmaceutical Waste," United Kingdom

18 Boston Area Chapter, 2006 Vendor Night, Gillette Stadium Clubhouse, Foxboro, Massachusetts, USA

19 Argentina Affiliate, Educational Activities, "Modulo 5: Definicion de un sistema integrado Generacion/Distribucion" and "Microfiltracion aplicada a un sistema de aguas, filtracion esterilizante," Hotel IBIS, Buenos Aires, Argentina

19 DACH Affiliate, Workshop, Biberach, Germany

19 France Affiliate, MES/EBR Conference, France

19 New Jersey Chapter, Hot Topic Session, "Productivity Improvement within Pharmaceutical Industry," Holiday Inn, Somerset, New Jersey, USA

19 San Diego Chapter, CIP Workshop and Dinner Meeting, TBD, California, USA

24 Greater Los Angeles Area Chapter, Commuter Conference, California, USA

26 Argentina Affiliate, Conferencia Magistral, Congreso ETIF 2006, Hotel IBIS, Buenos Aires, Argentina

26 Nordic Affiliate, Seminar, "Freeze Drying," Sodertalje, Sweden

26 Puerto Rico Chapter, GAMP Forum, Puerto Rico, USA

November 2006

5 - 8 2006 ISPE Annual Meeting, Walt Disney World Dolphin, Orlando, Florida, USA

9 UK Affiliate, Annual Awards Dinner, "Opportunities in UK Pharmaceuticals from Discovery to Manufacture," The Royal Bath Hotel, Bournemouth, United Kingdom

13 Chesapeake Bay Area Chapter, Bio-Showcase, Hilton, Gaithersburg, Maryland, USA

14 Delaware Valley Chapter, Program Meeting, USA

15 Greater Los Angeles Area Chapter, CEO Night, California, USA

16 Ireland Affiliate, Takeda Plant Visit, Bray, Ireland

16 New Jersey Chapter, Hot Topic Session, "Product-to-Market," Holiday Inn, Somerset, New Jersey, USA

16 - 17 Poland Affiliate, Conference, "Pharmaceutical Development," Poland

21 - 22 Nordic Affiliate, PAT Conference in collaboration with Eupheps/IDPAC, Gothenburg, Sweden

23 Nordic Affiliate, Annual Meeting, "Improving Operating Efficiency by New Quality Management," Gothenburg, Sweden

December 2006

4 Greater Los Angeles Chapter, Commuter Conference, Technical Training Series: Compendial Water at Amgen, LA Area, California, USA

4 - 7 ISPE Brussels Conference, Sheraton Brussels, Brussels, Belgium

6 New Jersey Chapter, Holiday Event, Dinner and Dancing on the Bateux, New York, USA

6 - 7 ISPE/PDA Conference, "Challenges of Implementing Q8 and Q9 – Practical Applications," Omni Shoreham Hotel, Washington, DC, USA

7 Rocky Mountain Chapter Annual Holiday Party, USA

12 Delaware Valley Chapter Holiday Party, USA

14 Italy Affiliate, Christmas Night, Italy

Dates and Topics are subject to change

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