PHARMACEUTICAL ENGINEERING®

THE OFFICIAL TECHNICAL MAGAZINE OF ISPE

JULY/AUGUST 2014 VOLUME 34, NUMBER 4

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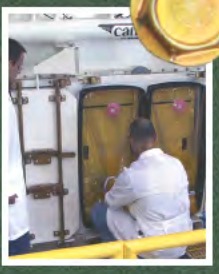

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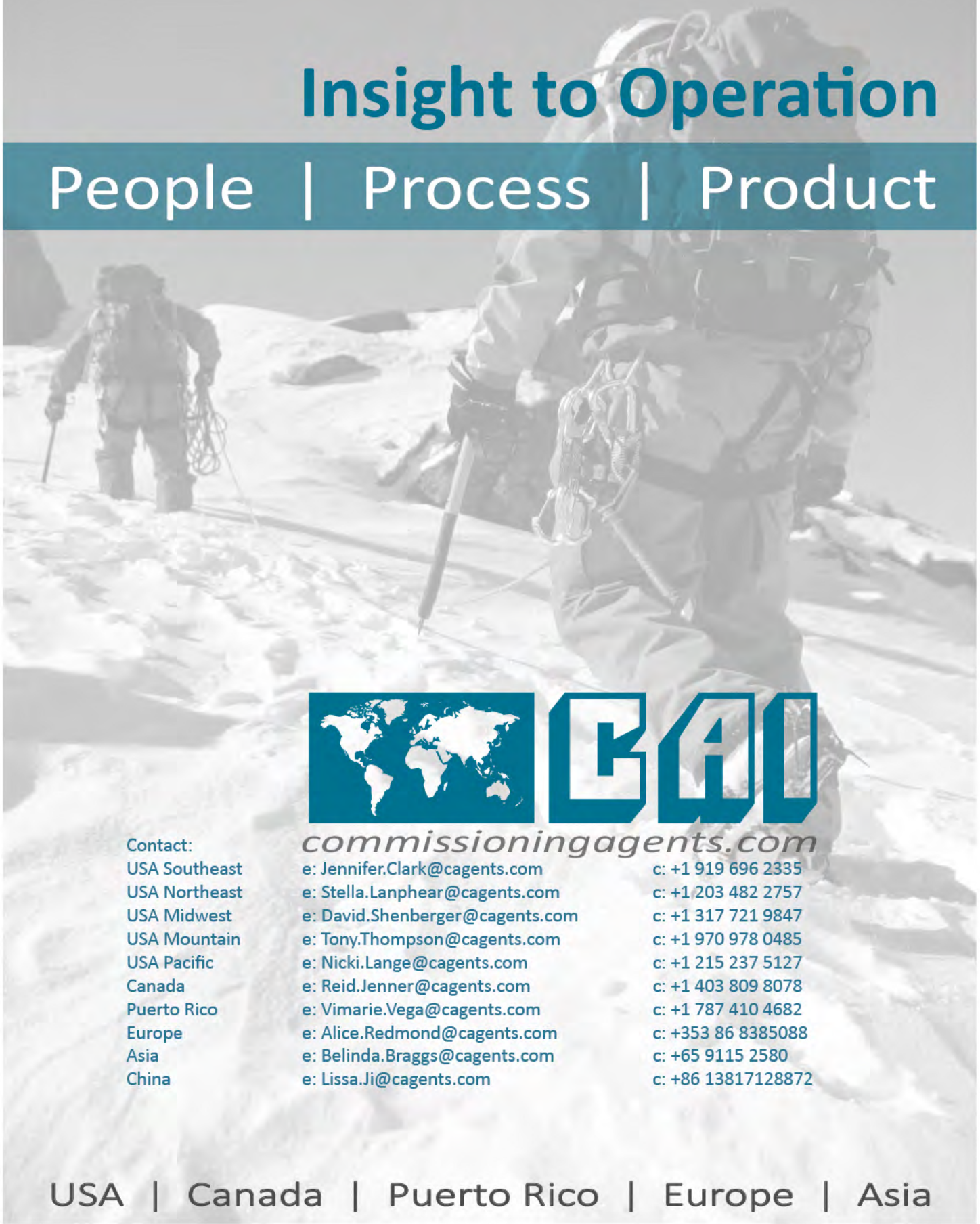

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This issue of *Pharmaceutical Engineering* features a variety of topics on the theme of next generation manufacturing, including innovative optimization strategies, advancements in measurement technology, and approaches to facility design. In addition to the technical articles, this issue will preview the 2014 ISPE Annual Meeting (see page 82), including an interview with Dinesh Thakur, Executive Chairman at Medassure Global Compliance Corp., formerly Ranbaxy's Director and Global Head, Research Information and Portfolio Management, who reported the company's failings to the US FDA. I am also excited to have had the chance to interview long time ISPE supporter Tim Tyson, Chairman and CEO of Aptuit, who recently chaired our CMO Executive Workshop. Tim speaks candidly about significant changes in the industry and ISPE's role in facilitating these changes.

The measurement of TOC is critical to the pharmaceutical industry because various regulatory bodies have established limits for TOC in Water for Injection (WFI) and other uses of water in manufacturing. Schmid and Turner present innovations in improving the accuracy and reliability of Ultra Violet (UV) oxidation direct conductivity Total Organic Carbon (TOC) measurement methods. The article discusses the possibilities and limitations of modern TOC instruments by means of concrete examples. The technical solutions presented are shown to improve the precision and accuracy of direct UV oxidation techniques.

Also on the topic of water technology, Cohen and Sackstein discuss the identification of problems affecting water systems with Reverse Osmosis (RO) and in the definition of the proper criteria of operation. The reliable and efficient operation of the Polyamide (PA) RO membrane is the main focus of this article, and a novel and innovative pretreatment system is presented, which meets the prescribed design criteria while providing effective results.

Foo, et al, describe the use of computer simulation tools for modelling pilot scale monoclonal antibody production in a contract manufacturing organization. In the case study provided, a pilot scale monoclonal antibody manufacturing process was modelled using an evaluation and optimization tool. In order to increase production throughput different optimization strategies, alternative process setups were proposed and evaluated. It was shown that the annual throughput of the plant could be increased significantly by reducing the minimum cycle time. This was made possible by using alternative equipment setups and utilizing idle equipment available in the plant.

In May/June 2014 issue of PE, Hettenbach described the background, design philosophies, and operating principles that can be used to design process transfer station and other process service rooms. In this issue, the second part of the article describes mother liquor transfer stations and solvent recovery and waste treatment area transfer stations, and covers topics including wall design principles, acceptable alternative standard approaches for process transfer stations, and layout considerations.

The Ballroom concept – defined as *"A large manufacturing area that has no fixed equipment and minimal segregation due to the use of functionally closed systems"* – also has been discussed in previous articles. Wolton and Rayner discuss the advantages and disadvantages of the concept and present an alternative approach. They study the lessons learned from the operation of recently commissioned facilities to predict what the next generation of disposables plant could look like. Will the "dance floor" concept be the next step in the evolution of fully disposable facilities?

I am also very pleased to publish an article by Jablonowski, Palovcak, and Wheatley, which represents the work of a student poster presentation. This describes a proof-of-concept study to determine the ability to target cancer cells through the attachment of a specific ligand to ultrasound contrast agents.

As always, I welcome your feedback – email me at ghall@ispe.org.

Gloria Hall
Editor, *Pharmaceutical Engineering*

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ISPE – Your Reliable Knowledge Resource

Berg reflects on her vision for ISPE and the organizational changes and initiatives that have yielded some significant accomplishments, including the Drug Shortages Prevention Plan and the Society's commitment to rapid response and quick program execution to become the leading resource for relevant information on scientific, engineering and regulatory issues.

While doing some spring cleaning in my office recently, I came across a copy of *Pharmaceutical Engineering* from March/April 2012 containing an article introducing me as ISPE's new President and CEO and summarizing my vision for ISPE. In this article, I discussed plans for refocussing ISPE around its core competencies and taking on key areas for strategic development. At the time, my goal was to help stabilize an organization that had been through rapid growth until it was hit hard by changes in the biopharm industry.

In the article, I wrote that "now" was the time for ISPE to shine brighter on the world stage and for our Members to be recognized for their important contributions. One of my early goals was to help ISPE more effectively communicate how pharmaceutical professionals and their companies work to ensure the quality and safety of medicines. Our plan was to leverage the talents and commitment of the 20,000 ISPE Members and to demonstrate their unparalleled commitment to quality through regulatory, executive and media relationships. As I look back on this goal, I recall the many organizational changes and initiatives that ISPE has undertaken, which have yielded some significant accomplishments.

Today, ISPE is on the world stage and highly respected for its leadership and professionalism. During the recent CMO Executive Conference in Baltimore, MD, USA, senior industry executive, Tim Tyson, CEO of Aptuit, described ISPE's position today as "having become a tour de force in the biopharm industry." Being there and seeing the nodding heads of Members, regulators and leaders, I knew that things had changed and that ISPE is on the path to even greater success. See page 38 for an interview with Tyson.

Many ISPE global initiatives such as the Drug Shortages Prevention Plan are being covered by international media. ISPE Members are being invited to join thought-leading regulatory and international policy discussions and ISPE's regulatory relationship activities have sky-rocketed as we are partnering with regulators who have the same needs for information as other Members. ISPE is the unbiased knowledge resource for the industry and our Affiliates and Chapters, Regulatory and Compliance Committee (RCC), PQLI and CoPs uniquely enable the delivery of that knowledge. Thanks to more than 4000 active Volunteers, your Society has changed and you are making a difference throughout the ecosystem.

In that 2012 article, I introduced three qualities of successful associations and plans to build those qualities in ISPE: 1) a reputation for good value and high quality programs, publications and services, 2) a contemporary, inclusive and enjoyable culture, and 3) a rapid response infrastructure that is able to collaborate effectively in order to seize opportunities. Scores of examples covered in my previous columns have recapped our progress. Moreover, with support of ISPE's Strategic Forum and Board of Directors, the commitment to rapid response and quick program execution has led to more timely events, training and hot topic publications that support the Society's mission to be the leading resource for relevant information on scientific, engineering and regulatory issues. Please plan to join us at the 2014 Annual Meeting in October where this conversation continues. See a preview of the 2014 Annual Meeting starting on page 82.

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Chemical and Media-Free Pretreatment for Biopharma RO – Electrolysis for Scale Precipitation and UV Dechlorination

by Nissan Cohen and Shlomo Sackstein

This article identifies the issues plaguing water systems with Reverse Osmosis (RO) and defines the proper criteria of operation.

Every system designer and end-user has to deal with many different criteria for the design and operation of biopharma pretreatment water systems. These criteria may include simplicity of operation, reliability, lower discharge of waste water or inexpensive lifetime costs.

As every system owner, operator, manager or design engineer has his own definition of what is an important criterion and what is not, it may be hard to identify accurately all priorities.

This article will focus the discussion on identifying the issues plaguing water systems with Reverse Osmosis (RO) and defining the proper criteria of operation. The RO membranes commonly have incorporated Polyamide (PA) as a main constituent which is sensitive to oxidation by free chlorine.[1] The reliable and efficient operation of the PA RO membrane is the main focus of this article.

A new system for pretreatment of pharmaceutical water systems will be presented that meets the prescribed design criteria with simplicity while providing effective results. This system operates without chemicals, media, or resins, and eliminates the need for regeneration, complicated instrumentation, and feedback loops. The system operates with no moving parts and without need of rinses or back washes.

Background

The traditional pretreatment of pharmaceutical water systems has installed modules to reduce contamination, reduce or eliminate chlorine/chloramine and remove double valent ion scalants, before feeding the water to the Reverse Osmosis (RO) system.[2] This modular approach has been successful in treating raw water for pharmaceutical usage, but the costs can be substantial for continued operations, salt purchase/usage, regeneration, water rinses, brine disposal, filtration, chemical additions of metabisulfite and microbial control. The Thin-film Composite (TFC) membranes used in RO systems are susceptible to microbial contamination and often require these modular components upstream to remove microbials and other contaminants from the water.[1]

Classical Designs

Common Solutions for Preventing Scale Precipitation in RO Systems: the Use of Softeners, Antiscalants (AS), and Acid Addition

Softeners use sodium ion exchange resin beads. Calcium and magnesium ions are removed from the water and exchanged with sodium ions. Depending on the system, the total hardness can be reliably reduced to below 10 ppm as $CaCO_3$. Resin bead based systems utilize sodium chloride to regenerate ion exchange resins that are saturated with calcium and magnesium. The total regeneration cycle has a series of rinses with varying concentrations of salts in the effluent. Once exchanged, the calcium and magnesium are sent to the drain by water rinse.

Often, the best operated softener system has wastage of

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fresh water needed for rinses. This intrinsic waste stream can vary from 5 to 25%[2,3] of total water volume depending on the incoming water hardness levels.

Local laws govern the disposal of salts and waste water disposal sent to the sewer; often a permit is needed for the disposal from the local Waste Water Treatment Plant (WWTP).

Runoff streams from the pretreatment and RO modules can be treated in the following ways:

- Collection and off-site disposal
- Treatment onsite to concentrate the solution for further disposal
- Drainage directly to municipality sewer with no further treatment
- Combinations of the above, dependent on conductivity

In addition to possible problems with effluent disposal, softeners filter out water borne contaminants. Organic resins can provide an environment for microbial growth due to the temperature and nutrient rich environment which often needs to be controlled. A sanitant, with a residual effect, is commonly added in the water. Oxidizers such as free chlorine or chloramine, are commonly administered for microbial destruction.

Chlorine/chloramines are not always an effective solution as the softener resin beds tend to channel. Channeling is a common phenomenon, in loose filtration media, as the water flow causes channels to develop which lessens the residence time in the media, causing diminished efficacy. When there is an appreciable build up of contaminants or thick biofilm, channeling can be affected. In this case, the sanitant will flow faster on the clean side of the resin leaving the clogged areas less exposed to the cleaning action.

All ion exchange resins are sensitive to free chlorine/chloramine oxidation. Resin beads break down and disintegrate over time as a result of either friction or chemical treatment. If the microbial Total Viable Count (TVC) starts to rise, the typical solution is to raise the oxidizer concentration, which causes more rapid softener resin disintegration[2] with an increased viable microbial environment. This, in turn, pushes the users to increase oxidizer concentration and so a vicious circle of cause and effect is formed. This cause and effect mechanism can be averted, as will be seen later in this article.

Antiscalant (AS)

These materials are dosed on the RO feed. The AS is a surface active material that interferes with precipitation reaction. The reaction can be retarded by dispersion, threshold inhibition or crystal modification.[2] AS addition is not dynamically controlled online; it is susceptible to fluctuations in ionic feed makeup. Typically, even with good AS performance, this system will need more acid cleaning of membranes than a softener-based pretreatment.

Acidification

Acidification has many of the characteristics of AS, as the acid is added to the RO feed. This acidification destroys carbonate ions, and stops calcium carbonate precipitation. This can be very effective in preventing the precipitation of calcium carbonate, but ineffective in preventing other types of scale, such as calcium sulfate.

In addition to nearly all the drawbacks of the AS addition, the acidification causes an excess of carbon dioxide (CO_2) in the RO permeate. Acids and all corrosive materials need controlled handling, storage and transport making the usage of these chemicals less desirable.

Common Solutions for Chlorine/Chloramine Removal in Pre RO Modules are Active Carbon Filtration (ACF) also known as Granulated Activated Charcoal (GAC) and Sodium Bisulfite (SBS)

Active Carbon Filtration (ACF)

Water is exposed to active carbon which removes the oxidizing chlorine/chloramine. The filters can be of the cartridge type, but more commonly are granules (GAC) packaged in a depth filter. GAC, although an excellent medium for chlorine/chloramine destruction, is also an excellent medium for microbial growth. The GAC bed must be backwashed and heat sanitized with a frequency of every few days to inhibit and control bacterial growth.[2,3]

Heat sanitization is a proven option for microbial control via clean steam or hot water above 85°C.[3] The heat sanitized ACF can be a complicated unit, with a plethora of pneumatic valves, temperature transmitters, pressure gauges and software needed for performance and documentation of the sanitization subroutine. In pharmaceutical pretreatment schemes, the ACF tank is usually manufactured from stainless steel. Typically, 316L stainless steel tanks are expensive to install.

Sodium bisulfite (SBS)

SBS is added to the feed water to remove free chlorine and chloramine. The reaction is fast, but an overdosing of two or three times above what is needed, is common. This safety factor is needed as the instrumentation has been known to drift, mixing may not be ideal, and other inaccuracies are possible due to fouling of the electrodes.

Without adequate chlorine/chloramine removal RO membranes are susceptible to damage. Inadequate or deficient sodium bisulfite administration can contribute significantly to membrane degradation.

Additionally, the constant overdosing of SBS can cause residue build-up on the membrane surface causing susceptibility to bacterial infestation of the membrane.

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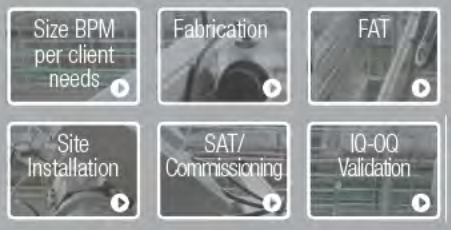

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Common Solutions for Sanitization: Chemical Dosing

One of the most effective types of sanitization is the use of hot water. Some pretreatment systems are poorly suited for hot water sanitization as the piping and equipment is based on plastic polymers of PVC and other non-metallics.

Often, sanitization for city water and pretreatment is chemically based. Chemical sanitization can have many drawbacks. Some drawbacks can be the handling of dangerous chemicals, post sanitization validation, manpower involvement, and unconfirmed results. If the system is usually biofilm-free, chemical sanitization can be effective. If the system has a developed biofilm, chemical sanitization may or may not be effective. Dosing, time increment duration, design issues of dead legs and stagnant flow areas need to be thoroughly investigated after sanitization administration.

New Design

Solution for Preventing Scale Precipitation in RO: Electrolytic Scale Reduction (ESR)

ESR

This unit is composed of a metallic cylindrical reaction chamber with flow-through water from the top to the bottom of the cylinder. In the central axis of the cylinder, an electrode is installed and connected to a positive electrical pole, while the cylinder circumference body is connected to the opposite negative electrical pole. Thus, an electric field is generated between the central electrode and the cylinder. This field causes current to flow between the central electrode and the metallic cylinder body. The current dissociates the water to OH^- and H^+ ions.[7] As a result, a low pH is formed around the central anode/electrode and a high pH around the cathode/cylinder. The high pH near the inside surface of the cylinder will cause scale to precipitate from the water, collect on the cathode, and it settles to the bottom of the reaction chamber. The amount of scale is small and typically will be in the range of 2 to 6% of total $CaCO_3$.

In an electrolytic cell, such as the above, low voltage direct current creates a positive electrical pole (anode) and a negative pole (cathode). In the presence of electrically conductive water, hydrogen ion and oxygen are formed at the anode and hydroxyl ion and hydrogen are generated at the cathode. A cathodically formed hydroxyl ion has the ability to greatly accelerate formation of calcium carbonate. Formulation of calcium carbonate ion clusters and nano-crystals are selectively diverted to the cathode. This formulation subverts bulk phase nucleation and limits both nano-crystal size and age.

The following equilibrium denotes the chemical reaction:

$$CaCO_3 + CO_2 + H_2O \leftrightarrow Ca^{2+} + 2HCO_3^-$$

$HCO_3^{-1} + OH^{-1}$ (hydroxide ion from strong caustic or electrolytically formed) $\leftrightarrow CO_3^{-2}$

$$Ca^{+2} + CO_3^{-2} \leftrightarrow CaCO_3$$

As shown above, the hydroxyl ion reacts with the bicarbonate ion to form carbonate ion.

The extreme insolubility created at the cathode and the power employed to drive the electrochemistry focused at the cathode produces rapid formation of very small crystals of calcium carbonate. Under such conditions, a tightly packed array of closely bound crystals cannot form. Deposition in an electrochemical precipitation cell tends to be soft, porous, and voluminous. The porous nature of deposition on the cathode does not retard electrolysis or migration of hardness ions. This allows the electrochemistry of precipitation to proceed unhindered even when sizable amounts of scale are deposited.

The water produced, after the selective precipitation of scale, is not defined as "soft" water as the output usually contains more than 100 ppm hardness.

So, What Have We Achieved?

We have achieved *kinetics modification* to slow precipitation to the point where deposits appear not to form. Because some of the scale has been removed from recirculating water, the *kinetics* of scale formation has changed even though scale could still form under certain conditions. The water is not soft at the outlet of the ESR; however, the scale forming ion content has been reduced to a level that has changed the period of time needed for hardness precipitation. If the system has been designed for the water to exit the RO membranes before the hardness has had time to precipitate – no scale will form in the RO membranes.

The ESR will precipitate *all* scale forming ions, not just magnesium and calcium, but any other trace ions that are susceptible to precipitation from the liquid at high pH, for example: silica, barium, manganese, iron, etc. Removal of only a small amount of the most problematic scaling ions will inhibit hardness crystal formation in the RO. This strategy works well for systems where water retention time, or flow-through, is relatively short. If water is retained too long in the RO, precipitate of scale will occur. If the ESR is improperly sized, scaling will form on the membrane reject surfaces and buildup on associated piping may become significant. This technology is well entrenched and proven in the cooling tower ion removal.

The electrolytic method for industrial RO treatment is well established with more than 100 worldwide installations. In addition, free chlorine is generated in the ESR as a byproduct.

The following equilibrium denotes this reaction:

$$Cl^- + H^+ \rightarrow HCL$$

$$HCl + HCl \rightarrow Cl_2 + H_2$$

This free chlorine by-product is a natural occurring factor keeping the ESR clean of biofilm.

Removal of Oxidants in RO Feed Water by Way of UV Irradiation – Hydraulic Oxidant Deactivation (HOD)

It is common knowledge that UV radiation will reduce concentration of free chlorine and chloramines.[5,6] UV breaks the chemical bonds of free chlorine or chloramine to form hydrochloric acid and other byproducts. When irradiated with a sufficient dose of UV, the reaction for free chlorine, as hypochlorous acid, is as follows:

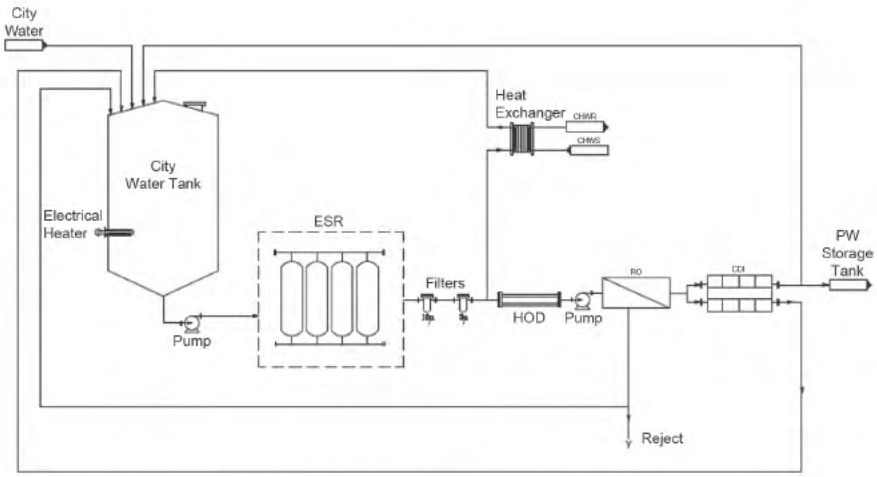

Figure 1. ESR and HOD configured in system.

$$2HOCl \rightarrow 2HCl + O_2$$

When irradiated with a sufficient dose of UV, the reaction for water containing chloramine and free chlorine, as hypochlorous acid, is as follows:

$$2NH_2Cl + HOCl \rightarrow N_2 + 3HCl + H_2O$$

The reaction for reduction of free chlorine in the hypochlorous acid form:

$$2HOCl \rightarrow 2HCl + O_2$$

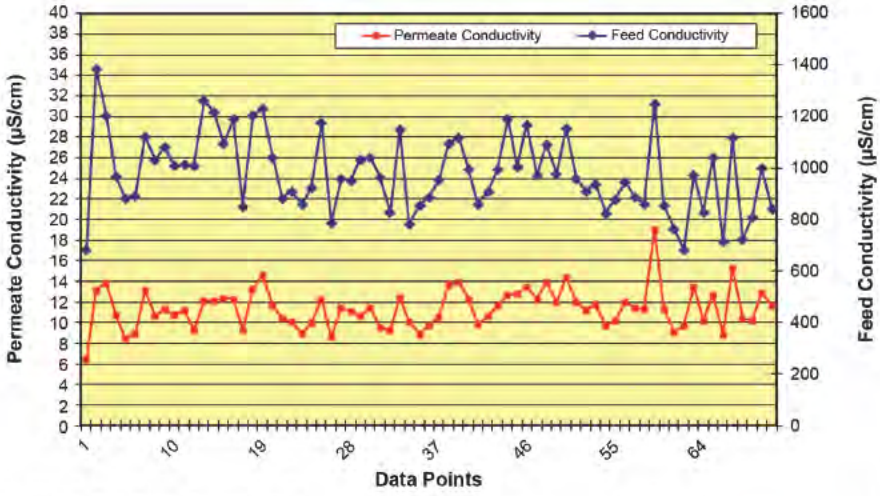

Figure 2. Conductivity over time.

The reaction for reduction of free chlorine in the hypochlorous acid form:

$$2NH_2Cl + HOCl \rightarrow N_2 + 3HCl + H_2O$$

The by-products of the reactions are easily rejected by the RO membrane.[5]

In effect, the HOD has removed the oxidizing substances in the water which could damage polyamide membranes, allows ion passage through membranes, and/or prevents damage to the downstream Continuous Electrical Deionization (CEDI) unit.

ESR and HOD in a System

Configuration

How are these complementary technologies integrated?

As we can see in Figure 1, the ESR is mounted as the pre-RO treatment stage ensuring the RO will not suffer scale while the HOD removes the chlorine/chloramines from the RO feed water. This dual approach system, comprising the ESR and the HOD, can ensure the city water will not cause RO blockage or decomposition of the membranes, and will provide chlorine/chloramine removal without traditional chemicals or organic media (GAC).

Some advantages are immediately gained, as both the ESR and HOD modules are fabricated out of heat resistant materials (SS and Quartz). Hot water sanitization for both modules can be employed reducing any possible microbial biofilm development.

The ESR and HOD modules prevent entrapment of free-floating bacteria and biofilm development, as no extraneous organic media (GAC), no resin beads, and no chemical additions are entrained in the pretreatment system.

Continuous Bioburden Reduction

The supplied ESR and HOD pretreatment modules are not susceptible to bioburden, as previously stated, as all the surfaces are manufactured of SS or quartz and are easily hot-water sanitizable. The addition of a hot water retention tank, heater, and heat exchanger with the proper sanitizing time duration protocols will enable a bacteria-free or bacteria-reduced environment, thus, placing less stress on downstream water treatment modules.

The ESR and HOD will reliably reduce incoming bacteria counts because of the free chlorine by product in the ESR and the high levels of UV radiation in the HOD.

Case Study

The ESR-HOD pretreatment combination was studied over an eight month period.

Figure 2 shows the conductivity over time. The X axis data points are the consecutive numbered dates that the readings of conductivity were recorded. The top graph scale is read off the right axis, the range of incoming conductivity is from a minimum of 700 µS/cm to a maximum of 1400 µS/cm.

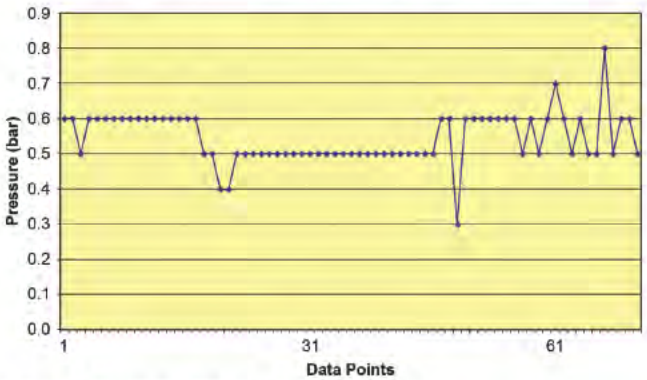

Figure 3. Pressure drop on the membranes.

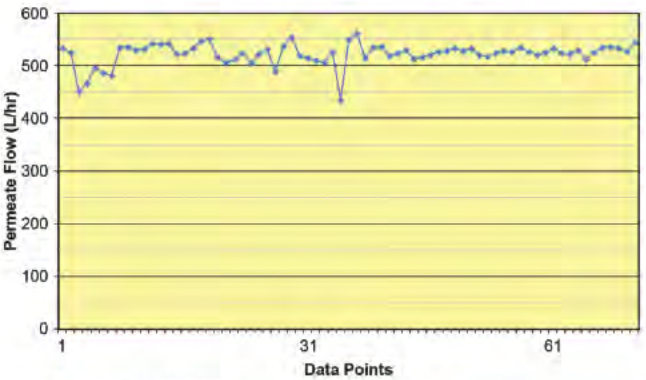

Figure 4. Permeate flow.

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	Micro Total count CFU/ml		E. COLI CFU/100 ml		Pseudomonas CFU/100 ml		Coliforms CFU/100 ml		Fungus CFU/100 ml	
Position in System	Average	Range	Average	Range	Average	Range	Average	Range	Average	Range
City Water Inlet	158	0 - 780	47	1 - 227	24	0 - 82	201	28 - 910	13	0 - 48
Exit City Water Storage Tank	1.27	0 - 10	0	0	0.167	0 - 1	1.375	0 - 11	0	0
Inlet to HOD	0.5	0 - 3	0	0	0.167	0 - 1	0.25	0 - 4	0	0
After HOD	0.05	0 - 1	0	0	0.167	0 - 1	0	0	0.167	0 - 1
After RO	0.05	0 - 1	0	0	0	0	0	0	0	0

Table A. Site microresults from a two month period of PQ.

Note: the permeate output conductivity closely follows the inlet conductivity. No clogging or perforation of the membrane is apparent after eight months of operation.

Figure 3 shows the pressure drop on the membranes. The X axis **data points** are the consecutive numbered dates that the readings of differential pressure were recorded. Note: there is little change in differential pressure over time. No clogging or perforation of the membrane is apparent after eight months of operation.

Figure 4 shows the permeate flow. The X axis **data points** are the consecutive numbered dates that the readings of permeate flow were recorded. Note: there is little change in permeate flow over time. No deterioration of the membrane is apparent after eight months of operation.

Site data for bioburden reduction is seen in Table A. Note: the logarithmic reduction in all micro counts as soon as the water enters the system.

Note: the E. Coli and Pseudomonas were both measured per 100 ml and **not** per the usual 1 ml. If the system was evaluated per the usual 1 ml – no detections of Pseudomonas or any other specific species would have been made.

Cost Comparisons between ESR-HOD modules and Activated Carbon Filtration, Softener, Bisulfite

Table B and C are based on a system providing 7 M^3/hr (30.82 gpm) of RO permeate.

Comparison of total costs (CAPEX + OPEX) as a function of years of operation as seen in Figure 5. The horizontal axis in Figure 5 refers to time in years. The perpendicular axis is in US Dollars ($). The red line is the operating expenses over time including the initial capital expenditure of the ESR-HOD modules. The operating expenses over a seven year period are approximately $66,000. The Softener and GAC option in the green line shows a lower capital expenditure, but a much larger operating cost of $550,000 over the next seven years. The GAC + AS RO of the purple line shows a slightly lower capital expenditure, but very high operating costs of $1,150,000 over the seven year time period. The differential in operating expenses between ESR-HOD and traditional pretreatment systems can range from $500,000 to $1,000,000 over a seven year period using the above calculations of water pricing. Any increases in costs will

Table B. Pretreatment Options

Description	CAPEX $ (Estimate)	Yearly OPEX (Calculated)
ESR and HOD	$300,000	$9,443
Softener – Active Carbon Filter	$100,000	$77,974
Active Carbon Filter – 2 units AS RO	$136,000	$164,910

Table C. Input Data for Costing

Sample costs for:		
Water Prices	7.00	$/m3
Sewer Use Fee	0.00	$/m3
Cost of Labor	25.00	$/hr
Price for Spent Brine Disposal	0.00	$/m3
Price for Fresh Salt	0.23	$/kg
Ion Exchange Resin	5.71	$/liter
AC Replacement Cost	11.43	$/liter
Electrical Price	0.50	$kW/hr
Industrial Steam (NG/LPG Burner)	93.14	$/ton
Price per Filter	28.57	$/Unit
Price per UV Lamp	607.14	$/Unit
Price per Industrial 8" Membrane	850.00	$/Unit

Tables B and C. Cost comparisons between ESR-HOD modules and activated carbon filtration, softener, bisulfite.

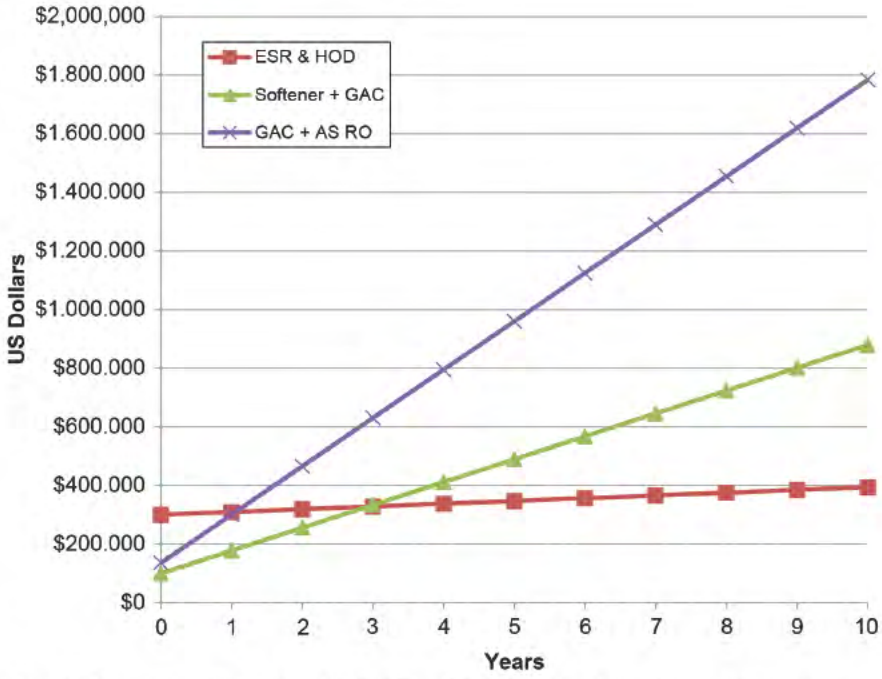

Figure 5. Comparison of total costs (CAPEX + OPEX) as a function of years of operation.

develop larger differentials as the ESR-HOD costs do not change overtime.

Conclusion

Installation of an ESR and HOD combination is a superior system with significant advantages when compared to traditional ACF, softener, and bisulfite installations. The advantages are: no chemicals, no media, no back wash, no regeneration and no waste stream.

The maintenance is minimal as the units have no moving parts. Operating expenses are immensely reduced compared with traditional pretreatment modules, showing savings of almost $500,000 to approximately $1,200,000 over a seven year period. The implementation of the ESR and HOD modules alleviates many of the limitations and operational problems of traditional pretreatment modules described in the first sections of this article. Performance of the ROs is enhanced by not using an-

tiscalants and bisulfite chemicals as pretreatment modules to the membranes. Continuous bioburden reduction by and throughout the system is exceptional and robust with the added feature of hot water sanitization when needed. The future for our industry lies with simple, reliable and "green" technologies. The ESR and HOD modules are "green" with no wastage, no disposal, no chemicals, no organics, no waste stream, with markedly reduced operating costs for the life of the installation.

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Transfer Station Design for Large Scale API Manufacture (Part Two)

by Joseph R. Hettenbach, P.E.

This article describes mother liquor transfer stations, solvent recovery and waste treatment area transfer stations, wall design principles, acceptable alternative standard approaches for process transfer stations, and layout considerations.

Part one of this article described the background, design philosophies and process bases and operating principles that can be utilized to design process transfer station and other process service rooms. In this article, there is a description of mother liquor transfer stations, solvent recovery and waste treatment area transfer stations, wall design principles, acceptable alternative standard approaches for process transfer stations, and layout considerations.

The article is geared toward larger multi-product API facilities – designed for the simultaneous manufacture of a number of products with equipment and piping set up in a *process train* fashion for each product. The following rooms or areas would be set up to achieve this capability; some of these may be combined together for economy of space, simplicity of function, etc.

Mother Liquor Transfer Stations (Rooms)

There are usually one or more in number of these type rooms. One such room could be named as **(MLTS-N)**; with N designating that the room services the north section of a large API facility. These rooms are used for the routing of mother liquors from product filtrations, and distillates from distillate receivers and to mother liquor tanks. In addition, solvent or water based waste streams from extraction and process cleaning operations, etc., can be transferred from reactors and other process equipment to operations for subsequent recovery, treatment, and disposal operations outside of the API building.

Nomenclature Notes

WWTP designates the wastewater treatment plant for the facility, which has weak and strong treatment facilities.

ML designates mother liquor tanks, which can be used to hold mother liquors from crystallization processes, various waste streams, requiring treatment prior to discharge to the wastewater treatment plant, and also distillates from batch distillation operations.

PTS-N Run1 and **PTS-S Run1** designates lines (runners) to allow transfer of process fluids to the north (N) and south (S) process transfer stations respectively.

MLTSR>S1, MLTSR>S2, and **MLTSR>S3,** designate connections to allow process streams to be transferred to treatment tanks S1, S2, and S3 respectively (located outside of the API process building).

Table A is showing an example of typical connections in a mother liquor transfer station.

Solvent Storage, Recovery and Waste Treatment Area Transfer Station(s)

In addition to the number of different type *process transfer stations* within the confines of the API building, solvent storage, recovery and waste treatment area transfer station(s) can be located either outside or in an enclosed room.

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Services	Conn.
To Weak WWTP	4
To Strong WWTP	4
From ML Tank 1	2
From ML Tank 1	1
From ML Tank 2	2
From ML tank 2	1
From BLDG Drain Tank (DT-1)	1
PTS-N Run 1	1
PTS-N Run 2	1
PTS-S Run 3	1
PTS-S Run 4	1
MLTSR > S1	1
MLTSR > S2	1
MLTSR > S3	1
Note: There were two Mother Liquor Transfer Stations in this particular example facility.	

Table A. Example of typical "connections in a mother liquor transfer station.

- New solvent unloading from tanker trucks into fresh solvent storage tanks
- Tanks to hold used solvent to be recovered or treated as hazardous waste
- Tanks to hold new and recovered solvents
- Bulk storage tanks for commodity chemicals, such as 50% sodium hydroxide, 37% hydrochloric acid, 99% sulfuric acid, acetic acid, etc.
- Lines, pumps, and connections to allow transfer of a number of fresh/recovered solvents to the process transfer station(s) to satisfy the current campaign needs
- Management of recovery/treatment operations such as distillation, steam stripping and other operations
- Provisions for offloading waste solvents and cleaning solution streams to tank trucks for appropriate outside disposal

Figure 1 is a photograph of a plastic model (scale: ½ inch = 1 foot) used for the design of a solvent area transfer station. This model also was used as a ready reference for the construction phase in the field. This particular one was for operations conducted outside (located in a warm climate area). This was one of the last two plastics models we made with an E&C company, before we started doing our facility designs using computer *3-D* design software.

Wall Design Development for Transfer Stations

The construction of the complete **index** (which specifies locations of connecting points) is done simultaneously in the piping design process – with the design of the wall faces, which contain (specify) the connection points. The design layout of these walls is quite complex. The interconnectivity of *services* and the desire for minimizing pockets and loops (i.e., maximizing top-down, gravity flow) must be considered. The relative locations of sets of connections points, e.g., feed lines to reactors, multiple solvent manifolds (overhead) and process fluids flowing from higher elevations (e.g., head tanks) and going to equipment at lower elevations (e.g., mother liquor tanks) have to be integrated in the wall layout. There also is the consideration to minimize the distance between connecting points (and the hose lengths required to make the connections.) It is good practice to reasonably manage these hose lengths and bad practice to couple two hoses together to cover long distances. Runners with connecting points are typically provided for longer horizontal distances, as well as using vertical runners to manage large height differentials (top to bottom) between the connecting points.

Once the index has been prepared, it must be thoroughly reviewed to ensure that all of the interconnectivity between all of the transfer stations envisaged has been accounted for. Some other connection points might have to be added, as a result of this review.

The next step is to review the ***wall designs*** (discussed above), which contain the exact location for each of the con-

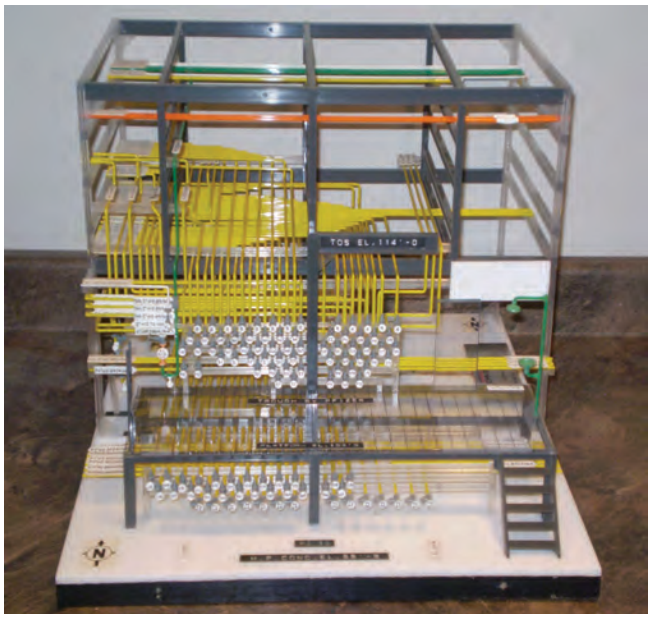


Figure 1. Photograph of a plastic scale model of a solvent area transfer station.

nection" (e.g., flanges on spools). To re-emphasize some earlier points, this is a very intensive, complex exercise – placing the connection points in spots and groupings to facilitate the setup the expected process operations. Again, *gravity flow* conditions should be achieved to the extent practicable, and manifold arrangements should be designed to minimize pockets and residuals.

Again, *pipe spool runners should be used* to allow the setups of pairs of connections points, which are greater than a standard hose length apart – the maximum length is typically chosen by the operations people, considering the weight, handling and maneuverability factors – typically not more than 15 or 20 feet. Obviously, it is not possible to satisfy all of the potential connection points, while following the set of concepts to adhere to and techniques to apply suggested in this article to use for the design of the transfer panel walls. Of course, *some compromises are therefore, inevitably required.*

As seen in Figure 2, a sketch of a *typical process transfer station wall face* (not "to scale") – showing a vertical section view of the rows of flanges on spools (coming through the wall) depicted by the **blue colored circles**, evenly spaced, in a typical triangular pitch pattern; located at two levels – a *grade* floor level and a mezzanine floor level.

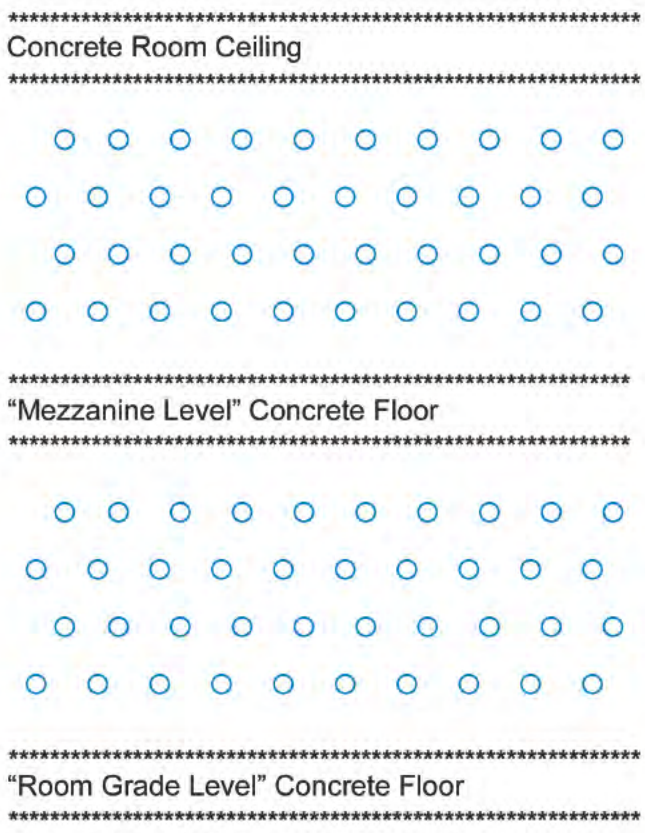


Figure 2. A typical process transfer station wall face.

Process Checks For the Transfer Station Designs

Once *all* of the connections have been located and checked on the transfer panels (i.e., the walls with the connection points containing the names of the specific services for each connection), the overall design of the process manifold should be tested for viability. Process challenges are made with the full set of hose connections required to run a selected number of representative processes, simultaneously. This would represent in a campaign mode set-up at least one of a number of possible ***product mixes*** projected to be scheduled in the facility. This check is for a number of processes to be run simultaneously (e.g., three or four different processes).

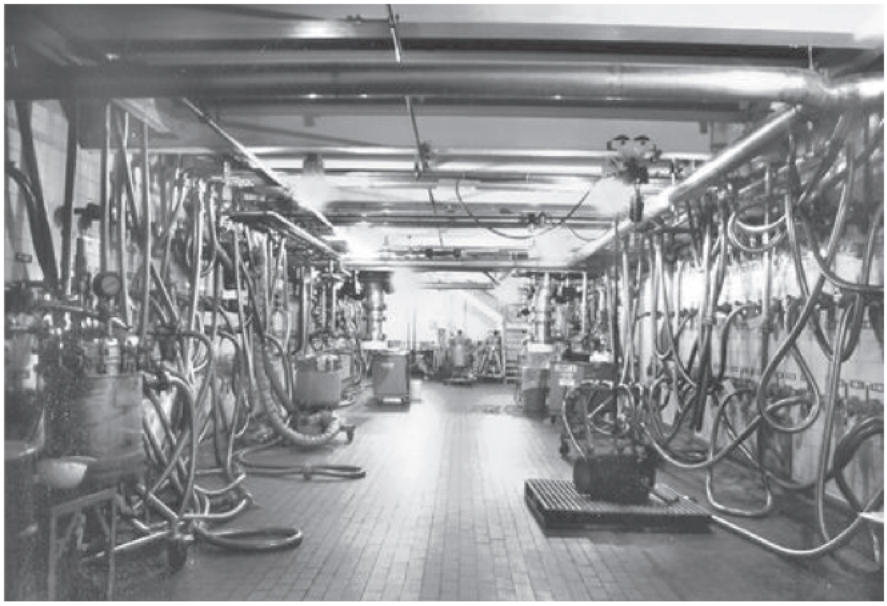


Figure 3. Main process transfer station in a 5 pool API plant set up for cleaning and process operations.

Once the overall design has been checked for suitability by process challenges, each connection can be given a permanent I.D. number/code which describes its location, including the wall, level, row and number in sequence on the row. In addition, an I.D. tag should be affixed to the wall describing what the service is, and what line number (passing through the wall ending in the flanged spool) that it is associated with. For example: "From Reactor No. 1, Line number *12345*."

General Note: some future spools should be provided as free space is available; in addition, the expected future lines should be designed for – with special allowance in the three dimensions including the detailed routing of these beyond the proximity of the outside of the transfer panel wall (reasonably) to facilitate the future piping required in that area which would be normally, fairly dense in space utilization due to the number of pipe lines, manifold piping, and automated valves, etc.

Depending on the number of connection points provided, some inlets and outlets to and from selected equipment pieces can be located at the other levels (upper or lower) to facilitate shorter hose lengths required for connections..

Adequate space should be allowed around spools (in **3-D**) to allow installation of mini-manifolds (to provide additional connections for a given process, as well as special devices, e.g. spec-free in-line filters for final API - Finished Goods (FG) process steps. Space also should be provided around spools to provide fittings with quick connects and manual valves for nitrogen (blowing) and water (flushing) of hoses. *It is imperative that hoses are blown clear and flush rinsed with water or other appropriate solvents/solutions, prior to disconnecting hoses during the cleaning and changeover operations.*

Utility stations also should be installed at each operating level including steam, nitrogen, and air services; there also should be a number of nozzles on pipe spools on the *transfer panel* walls for nitrogen, process water, and purified water (as applicable).

Process Cleaning Utilizing Process Transfer Stations

It is important to keep in mind that the set-ups required for *process cleaning* also must be accommodated. In many cases, the *set-ups for the process cleaning operations* can be a more strenuous, complex exercise than the set-ups required for actually running the processes. A further complication is that the specific processes generally have different campaign running times. It is expected that, generally, some processes will still be running, while there is process cleaning going on for those processes which have already finished their scheduled campaign.

Figure 3 is a photograph of the first level of an operating process transfer station set up for some cleaning operations (performed simultaneously along with other processes running). Note: the carts that are shown illustrate the set- up with hoses to allow the completion of cleaning loops, including the hoses used to run the process, as well a number of sparkler filters set-up at the grade floor level. This picture speaks to the need to provide adequate floor space to ensure safe and reasonably comfortable working floor space.

Acceptable *Alternative Standard* Approaches for Process Transfer Stations

There are cases, particularly involving expansions or up-

grades of existing facilities, where due to spatial constraints, and/or budgetary restrictions, some simplified approaches must be used for their design and construction of process transfer stations. The overall approach would be similar to that used for the *contemporary design* type approach, as described above. The following general principles could serve as guidelines for the development of an *alternative acceptable standard* type approach. Of course, it is desirable to have enclosed rooms when that is possible.

Layout Considerations

In cases where there is not ample space to provide an enclosed room, and without the ability to satisfy the other requirements associated with a room set-up, either open faced booths, or simple s/s constructed panels to hold the connections can be used.

In place of one or more process transfer station rooms, there would be a number of smaller local transfer stations with series of pipe runners connecting them. This approach would work better in cases where there is a decent level of semi-dedication of equipment, i.e., less flexibility built in for variable use of the equipment; this would reduce the numbers of lines and connections required in the transfer stations. This could take the form of having a selected number of reactors set up for use for batch make-ups, solids charging etc., and other reactors earmarked for crystallization service. Product isolation equipment- centrifuges and filters also could have mother liquor tanks and wash tanks pre-assigned to them. Adequate space and the proper equipment/systems must be provided for cleaning of the hoses and fittings scheduled for removal, following the process campaign.

Ventilation Considerations

Adequate ventilation should be provided in the area of the transfer station. Of course this is more easily achieved when a booth is involved. The objective is to minimize any pockets of solvent vapors, etc., that may result from some small leaks. Local exhaust type systems can be provided in the area of the connection flanges, taking care that the flows and pressures involved do not appreciably upset the intended normal room ventilation design conditions – which is, in practice, a bit of a challenge.

Containment Considerations

Booths can be provided with solid floors, pitched to floor drains. In the cases of open floor transfer panels, it is best to provide some curbing and a solid floor surface, again, pitch to floor drains, to provide some level of containment for

liquid spillage. A level detection instrument can be added in a small well (trap) designed for that purpose to alarm a spill condition. Of course cameras in the areas sending pictures to a control room would provide another means to monitor the area.

Housekeeping Considerations

Care must be taken to keep hoses out of any aisle ways, so as not to obstruct normal traffic in the area. The hoses also should be arranged in an orderly fashion, and properly supported, when the connections are made during the setup for the campaign to facilitate the disconnection operation. The area should be inspected on a regular basis – small drips and leaks and vapor smells can be taken care of, before they become more substantial. Hoses, fittings, etc., for use on the transfer panels should be stored and organized in a location which will not upset the normal operations in the area – in a storage room remote from the transfer station if necessary (and labeled for ready identification).

Safety Considerations

Transfer stations out on the open process floor, inherently have less containment attributes. The cleaning and disassembly of hoses and fittings after a campaign requires adequate space and set-ups appropriate for that task. Hoses connected to flanged spools on a campaign basis, are more apt to have leaks than process piping which is permanently installed, had been pressure tested, etc., this is particularly true for Teflon-lined piping systems. The occurrence of spills and leaks that are in open areas, requires greater care in management of these potential upset conditions, than in closed rooms. Vapor leaks can be the source of other problems in the operating area, as well as exposure to operation personnel. Specific chemical species devices (instruments) as well as more general type monitors with alarms should be considered to warn of the leaking situation.

Summary and Acknowledgements

Process manifold rooms or transfer stations are important components of large, flexible multi-product API facilities. The design of these type facilities requires careful planning, and attention to detail to satisfy processing, operational and product quality requirements. At the same time, safety, environmental, health, and maintenance needs must be accommodated, while following the CGMP guidance as it applies.

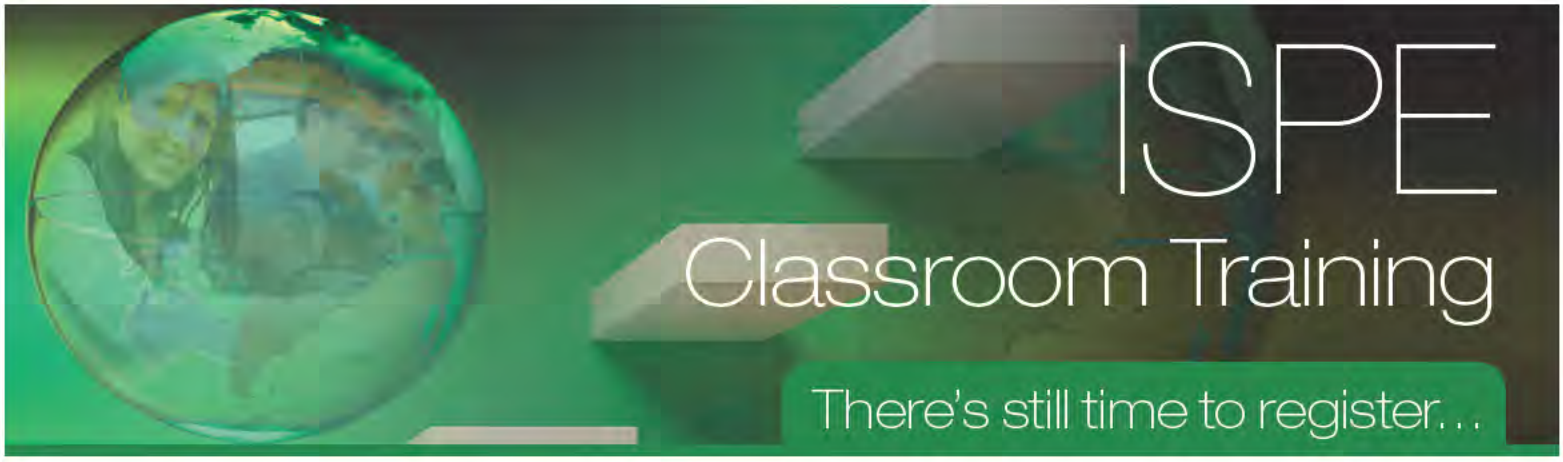
The scope for the design of transfer stations for large scale API manufacturing facilities includes:

- Process evaluation for the products to be manufactured, and establishment of the equipment list, piping and instrumentation and control requirements.
- Development of an *index table* to define all of the connections required in all of the transfer stations described in this article to ensure the connectivity and flexibility required.
- Develop the layout of the transfer station walls, together with the detailed process piping design including lines to and from all of the transfer stations; and the remainder of the detailed piping design, associated with the specific equipment.

The guidance set forth in this article is based on the successful design, construction and operation of some 50 transfer stations over a period of 15 years. These transfer stations, located in a number of facilities in the U.S., Puerto Rico, and Singapore, were developed (working on the details, hand-in hand with the writer of this article, who actually did the wall layouts) with a number of highly skilled piping designers, many of whom contributed greatly to the development of these design principles. The key players in this evolving design effort were Richard Piazza and Richard Molinaro (both now deceased); Roger Desroches and Richard Chou – all of these fine professionals were of the vintage "Crawford & Russell – John Brown Inc. – Kvaerner Inc." lineage. Much of what I know and learned about detailed piping design and API facility layout came from working over many years, on a number of API facility projects with these exceptional professionals. Improvements and refinements were made over the years learning from the performance of and experience with the units designed for earlier projects, using basically this same team of designers, without whom, the program would not have been as successful.

About the Author

Joseph R. Hettenbach has more than 35 years of process engineering and environmental engineering experience, spending 33 years at Pfizer Inc, servicing manufacturing and research facilities in many U.S. locations, Puerto Rico, Ireland, England and Singapore. He has managed the detailed process design of a number of projects for laboratory development, kilo plant, pilot plant and commercial scale manufacturing API facilities. He has made presentations on the subject of "improving the process design of multi-product API facilities" to a number of E&C, A&E and CM companies throughout the U.S., in Singapore, and in Ireland; to ISPE and to the AICHE. He has Masters degrees in chemical engineering and environmental engineering from Manhattan College. He is a licensed Professional Engineer in New York State. He also has taught as an adjunct professor in the Graduate Environmental Technology Program at the New York Institute of Technology. He can be contacted via email: tjchett@optonline.net.



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Lessons Learned in the Ballroom

by David A. Wolton and Andy Rayner

This article presents an alternative approach to the ballroom concept. It studies the lessons learned from the operation of recently commissioned facilities to predict what the next generation of disposables plant could look like. Will the "Dance Floor" concept be the next step in the evolution of fully disposable facilities?

Previous articles and seminars[1] have discussed the advantages of using the "ballroom concept" for the layout of biopharmaceutical bulk biologics production facility design, using both stainless steel and single use equipment. This article will evaluate the strengths and weaknesses of this approach with regard to single-use equipment based facilities now that the concept has been used to a greater and lesser extent in recently commissioned facilities. It also will seek to learn from these experiences and propose an alternative dance floor concept; that could result in a leaner, smaller, standardized facility, more suited to repeatable, reliable, high performance manufacturing.

Advantages of the Ballroom Concept

Definition of the ballroom concept is:

> *"A large manufacturing area that has no fixed equipment and minimal segregation due to the use of functionally closed systems."*[2]

Ideally, using the ballroom concept would result in a totally open production space where media preparation, buffer preparation, cell culture, purification and final filtration would all take place in the same room. However, most "ballroom" type facilities built recently have stopped short of the full implementation of the concept - *Figure 1*.

These improvements have the following advantages:

- **HVAC Cost Saving** – by containing the equipment, the surrounding area can be reclassified. This has a significant impact upon HVAC annual running costs as the higher the classification the greater the energy usage. (33% reduction in air supply for the classified space).[3]
- **Open Area** – *a large open area where all skids are on wheels allows for rapid reconfiguration of the facility, easy cleaning and fast construction.*

All of these advantages have made the construction of ballroom style facilities increasingly popular, especially

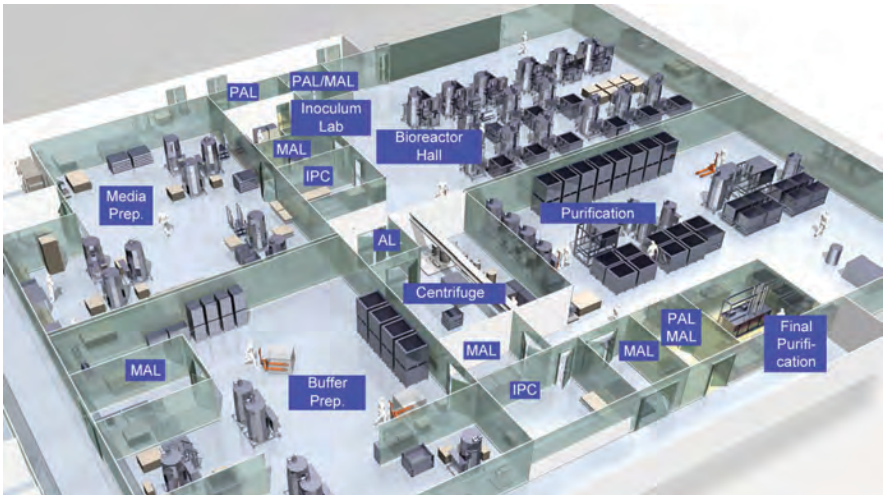

Figure 1. 3D model of a ballroom type facility.

when coupled with disposable technology. Recently however drawbacks have started to surface as a result of operational reviews (such as those undertaken using lean six sigma).[4] For in-market supply, where reliability and repeatability are key, another approach may be preferable.

Lessons Learned From Implementation of the Ballroom Concept

Movement of Totes

In the last 5 years, plant designs have shown significant decreases in facility footprint compared to traditional plants. These designs have incorporated many of the ballroom concepts including functionally contained systems. These facility designs also have relied (in most cases) on the physical movement of totes from the media preparation areas to point of use. It is now being realized that this movement is:

- A "non-value add" operation and is in effect Muda (wasted effort).
- Moving hundreds of pounds of weight can often be challenging and require special safety accommodations

Use of Mobile Totes for Transport of Bags

When it was first introduced, one of the big advantages of disposable bag technology was its mobility. Processes could be changed without the need for expensive modifications of the facility. The disadvantages of this mobility were seen as irrelevant until operations personnel in commercial production facilities started to focus on reliability and repeatability (typically using operational excellence approaches, such as lean six sigma), this resulted in the following disadvantages coming to light:

- Increased possibility of mix-up
  - By taking away the fixed pipework normally associated with stainless facilities, the disposable facilities have removed a physical "layer of defence."[5]
- Large tote storage areas and wider walkways
- Potential for tubing on the floor/trip hazards

Customization of Disposables

In the beginning, the end user really appreciated the ability to customize their equipment; however, as the use of disposables has become mainstream, this customization has started to cause problems; especially for the supply chain. It is known that the customization of parts results in:

- Increases risk of stock-out
  - Stock-outs can be mitigated in many ways; however, if parts become an "off the shelf" item in the future, all end users will benefit.
- Larger volumes of inventory
- Higher cost

...the dance floor concept (a smaller and more defined space) is being considered as an alternative to the ballroom concept...

Has Flexibility Gone Too Far?

There has now become a realization that market supply/phase III a more reliable, effective and efficient production operation is required and some of the "fully" flexible approaches may need to be revisited. In exploring the potential for a more optimal approach, the dance floor concept (a smaller and more defined space) is being considered as an alternative to the ballroom concept and this alternative is described below.

The Dance Floor Concept

It is important to note that disposable mammalian cell culture facilities are limited in size to ~2 to 4 kg per batch. If

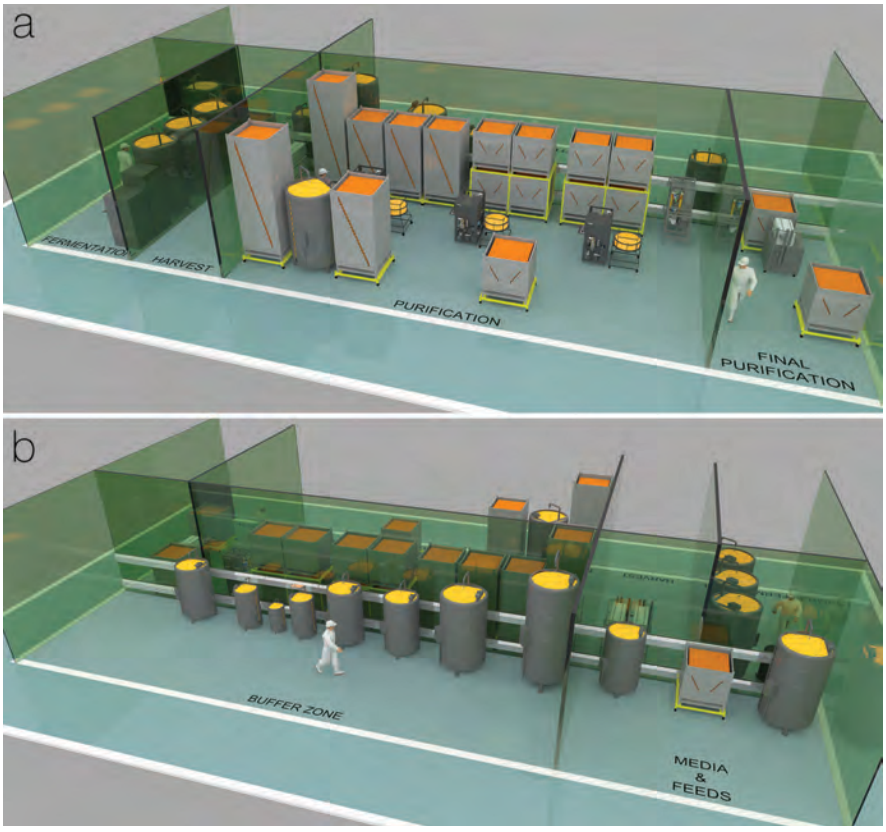

Figure 2a. View of the dance floor (3 × 2,000 L bioreactor) from the reactor hall areas.
Figure 2b. View of the dance floor from the buffer/media preparation areas.

quantities greater than 4 kg per batch are required, a stainless steel facility may be chosen. Modelling during the concept design phase will help the client make these decisions. Recent plant designs have positioned the media and buffer preparation facilities adjacent to the manufacturing operations - *Figures 2a and 2b*. This allows direct transfer through the wall to the production equipment and avoids movement of totes. This concept has developed into the philosophy of the 3m rule.

Definition of the 3m Rule

"Wherever possible, equipment should be static (in use) and situated no greater than 3m from its associated equipment."

The 3m rule has had a number of beneficial knock on effects:

- Reduction in operator error
- Reduction in tubing length/waste
- Storage vs just in time
- Fitting the facility around the equipment rather than the equipment around the facility

Figure 3 shows a close up of the three 2,000 L bioreactors. The bioreactors are clustered together to minimize tubing length and provide routed tubing paths. Note: the 2,000 L reactors can be clustered close together because there is not the need for the maintenance access of the equivalent stainless systems, also the equipment can be moved periodically (when empty) to facilitate cleaning.

Reduction in Operator Error (Poka-Yoke)

With some production steps, for example Protein A, there are a significant number of sequential additions. When mobile totes are used, it increases the risk of a mix up. Manual checks are often put in place to mitigate this, for example, conductivity checks; however, sometimes these systems fail. There are other ways of avoiding mix-ups:

- Color coding
- Defined tubing routes
- Automation

By making the systems static, all three of these mitigating measures become available. A 3D interpretation of the defined tubing routes concept is shown in Figure 4 (along with a "draw bridge" which swings into place when totes are in use).

Automation

The level of automation is dependent upon the end users requirements. If the plant needs to be very flexible, auto-

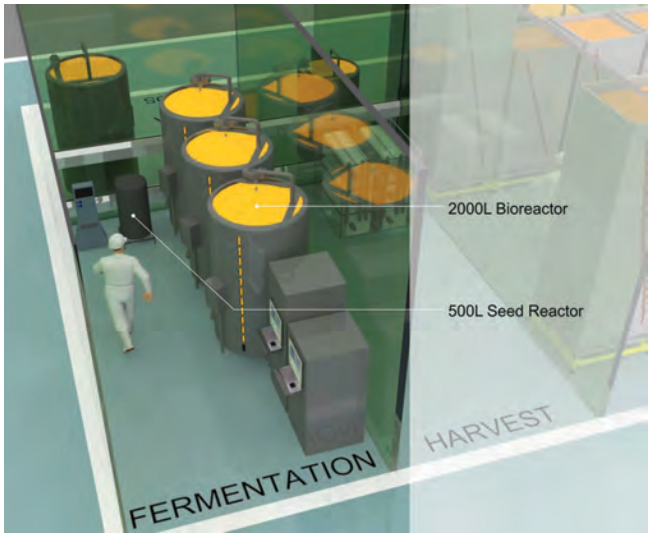

Figure 3. Three 2,000 L bioreactors with associated seed reactor.

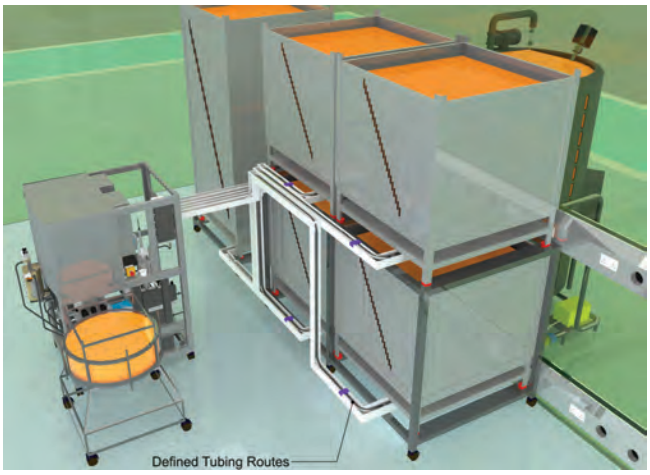

Figure 4. Defined tubing routes and the "drawbridge" used to connect to the chromatography control skid.

mation may not be desirable; therefore, color coding and defined routes used instead. However, if repeatability is key (i.e., in market supply), automation could be desirable. In stainless steel facilities, it is normal to link skids (e.g., Protein A chromatography controller skids) to systems like:

- Distributed Control Systems (DCS)
- Manufacturing Execution Systems (MES)
- Supervisory Control and Data Acquisition Systems (SCADA)

These computer control systems control the whole process and data within the facility. This is not normally done in disposable facilities, mainly due to the mobile/simple nature of the equipment. If the equipment becomes static, this can change.

Figure 5 shows a pinch valve next to an Iris valve (the Iris valve closes around the tube as it passes through the wall between buffer and purification). By defining the tubing route from the buffer preparation system to the pinch valve, the computer then knows what buffer is being made (using an MES system), what tank it is being made in (via the load cells on the buffer preparation skid), what route it is taking (via the peristaltic pump and the pinch valve), and what bag/tote it is filling (via the routed tube). As the tube from the buffer tote is routed to a specific port on the chromatography skid as seen in Figure 4, the computer then controls when that buffer is added to the process.

Reduction in Tubing Length

By changing the way the facility is designed (see section on fitting the facility around the equipment), engineers can focus on minimizing tubing length, thus reducing waste in the design phase.

Storage vs. Just-in-Time

By implementing the 3m rule, space around the production skids (e.g., Protein A) is at a premium. This can be solved in a number of ways.

Storage

- Racking is used to use all available vertical height - *Figure 4.*
- Multiple batch buffers – specific buffers can be chosen which have a long shelf life, these buffers are stored in tall containers that will last for a number of batches, the buffer is filtered in with a large filter and filtered out with a small filter. One outlet filter is used per batch to ensure the bag contents do not become contaminated. This approach not only reduces the amount of plastic waste, but also reduces cost, due to reduced preparation time, paperwork, dispensing and number of bags needed.
- If all avenues are exhausted, the buffer is stored in a mobile tote and wheeled to the skid.

Just-in-Time

- With most Mab processes, 2 to 6 buffers per batch can be made just-in-time and fed directly from the buffer preparation area to the chromatography skid. This reduces plastic waste by cutting out the need for a storage bag as well as the saving footprint needed for the storage tote.

Note: bioreactors can be filled directly from the media mixing systems and the media held in them prior to use, again negating the need for a media storage bag.

Fitting the Facility around the Equipment, Not the Equipment into the Facility

The introduction of standard disposable parts[6] has a positive impact upon defining the distance between equipment. It is

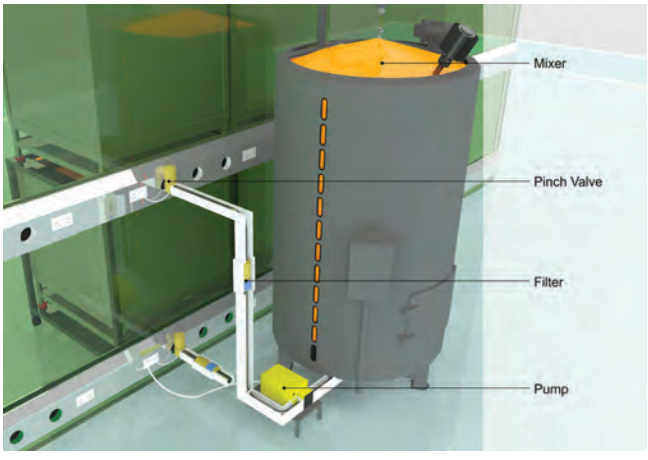

Figure 5. Use of pinch valves and defined tubing routes to control transfers through the wall.

now possible to put standard disposable parts on order while locking down the process flow diagrams. This allows the potential for early prototyping of the process, which in turn allows for resolution of ergonomic/lean/Poka Yoke issues earlier in the design lifecycle.

During prototyping, the final positioning of the internal walls between areas can be positioned for optimal use of space. The decisions here will be based on level of containment and client preference. Regarding client preference; having no walls between areas will normally be preferred by operations personnel (one team and easier communication); however, this approach is not widely seen in the industry to date. Note: it has been found that the use of glass significantly improves the communication between the areas, and is highly recommended.

The above can be coupled with 3D modelling to give a high degree of assurance that the facility will be both lean and ergonomic.

The Wheels Are Not Removed

Although there are defined paths for the tubing and ergonomic clustering of equipment, it is not envisaged that the equipment would become fixed. It is more akin to the super skid where if necessary, the equipment can be changed or relocated. Product change-over times will be increased (slightly) compared with the current highly flexible units; however, this will be outweighed by increased reliability and reduced size (and therefore running costs) needed for phase III and in-market supply. In effect the room will still be like a ballroom; just smaller.

Summary

- Leaner: minimal movement of totes, just in time production of media and buffer.
- Smaller: only space provided for ergonomic access, close proximity of all associated equipment, vertical height utilized.
- Standardized: use of standardized disposables where possible, only one way of assembling disposables, consistency of operation and simpler training requirements.
- Reliable: defined tubing routes, static equipment, recipe driven automation, central data gathering.

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David A. Wolton joined PM Group in 2012. In his position as Biopharma Consultant, he is responsible for process optimization with a focus on disposable applications. He has more than 25 years of experience in biopharmaceutical manufacture and was previously employed at CMC Biologics, Wyeth (now Pfizer), Elan, and Lonza. Wolton received a BS in microbiology from the University of Dundee. He can be contacted by email: Dave.Wolton@pmgroup-global.com.

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PHARMACEUTICAL ENGINEERING Interviews

Timothy Tyson, Chairman and CEO of Aptuit Inc.

by Gloria Hall

The Chairman and CEO of Aptuit speaks candidly about significant changes in the industry, his evolving leadership and management philosophy, ISPE's role with influencing change in the industry, and the challenges for industry to increase productivity and reduce risk.

Timothy (Tim) C. Tyson is currently Chairman and CEO of Aptuit Inc., headquartered in Greenwich, CT. His remarkable corporate career spans nearly 30 years in the pharmaceutical industry. His expertise in leadership and management is internationally recognized. From 2002-2008, Mr. Tyson served as COO, President and CEO of Valeant Pharmaceuticals International. During this period, sales grew 69% and earnings increased 135%. He led a major restructuring of the company and established a highly effective Research and Development capability which developed a best in class epilepsy compound and a promising pro-drug for hepatitis C, both in Phase III. Tyson is a 1974 graduate of the United States Military Academy at West Point. While on active duty at Ft. McClellan, AL, he earned a Master of Public Administration, in 1976, and a Master of Business Administration, in 1979, from Jacksonville State University. In 2002, Mr. Tyson received a Bicentennial Leadership Award from the United States Military Academy at West Point and was named 2007 Alumnus of the Year at Jacksonville State University. He has served on the board of directors for Valeant Pharmaceuticals International; the Pharmaceutical Research and Manufacturing Association (PhRMA); BICOM; on the CEO Roundtable for the University of California at Irvine; on the Dean's Executive Forum at Cal State Fullerton; the CEO Council on Cancer; the Health Sector Advisory Board at Duke University; the Leadership Forum of the International Society of Pharmaceutical Engineers and as a visiting lecturer at Cambridge University. Mr. Tyson has served on the board of directors for non-profit organizations in Raleigh-Durham, NC and Orange County, CA and with the United Way.

Tyson was instrumental in the creation of the CMO Executive Workshop held in Baltimore, MD, as part of the ISPE Pharma Quality Week. A select group of executives from Owner Companies, CMOs and Regulatory Agencies converged to collaborate on best practices for CMO-Owner relationships and processes. Attendees were charged with generating viable solutions to issues related to the

Selection, Start-up, Governance and Delivery Phases associated with CMO management. Their input will serve as the foundation for future guidance on CMO best practices.

You have had significant experience in all phases of the industry and marketplace over your 30 year career. Tell us about that experience and what you feel has been the most significant change in the industry?

The most significant change in the industry is the significant increase in difficulty in bringing new medicines to those in need.

The industry has gone through significant changes since I joined in 1980. It has been highly rewarding to be able to be a part of finding, making and delivering medicines to people in need that increase quality of life, extend length of life and to prevent treat and cure life threatening illnesses. The most significant change in the industry is the significant increase in difficulty in bringing new medicines to those in need. Even though the scientific knowledge has increased exponentially, the probability of finding and bringing a drug to market is essentially the same with even more hurdles. The evidence and cost have increased drastically, the regulatory scrutiny and requirements have become much more demanding and the technical challenges have exploded. All require more time, investment and scientific rigor.

How has your leadership or management philosophy changed over the years to adapt to the changes in the industry?

I have learned that it is all about people. It is essential to get the right people working as a team motivated to a common objective with an exceptional leader to deliver world class results. The politics and bureaucracy are lethal in the business and drug development world. I have learned that an organization is a reflection of its leadership and that highly motivated people working as a team can achieve the impossible.

You have been involved with ISPE for many years, what do think ISPE's role is with communicating and influencing change in the industry?

I am a strong supporter and advocate of ISPE. I have been a member since the early years and have always taken much more from the experience than I have been able to give back. ISPE represents a professional organization that provides excellent forums and tools for education, professional interactions, and informal discussions with regulators. ISPE also has exceptional resource documents with course booklets, white papers, baseline guides and so many other important references. ISPE has become the source of technical information for the industry.

Tell us what inspired you to take a leadership role in the development of the ISPE CMO Executive Workshop?

I have had great experience in all phases of the industry and have worked in owner companies and for contract service providers. This is a very important area as the amount of outsourcing continues to increase and as the impact has become much more strategic. I wanted to be a part of a seminal meeting that could provide some needed direction and connection of the owner companies, contract service provider and the regulators. I have found that all want to do the right thing and have common objectives. The amount of complexity and risk demands that a common understanding of the issues and the development of some concrete actions can make a major impact on reducing the complexity and risk. I strongly believe that outsourcing is strategically essential to the future of the industry.

Supply Chains are very complex with many CMOs. What do you perceive to be the biggest challenge and opportunity for industry to increase productivity and reduce risk?

The supply chains are extremely complex and challenging. The biggest opportunity to increase productivity and reduce risk is to establish a common quality systems approach to delivering outcomes that are recognized and agreed by all owner companies and all regulators. There are a number of issues to do this, but the benefits far outweigh the risks.

This conference is a key opportunity to influence specific actions to better understand the key issues affecting the outsourcing of development and manufacturing work. It is intended to develop a white paper and an industry baseline guide from this meeting.

I am confident that participants will gain a better understanding of the issues and can influence the development of a white paper and the initial baseline guide documents to provide the industry with a starting point to manage this important and complex activity.

Modeling and Uncertainty Analysis for Pilot Scale Monoclonal Antibody Production

by Noor Zuraihan Mohamad Noor, Ramlan Aziz, Badarulhisam Abdul Rahman, PhD, and Dominic C.Y. Foo, PhD

This article presents the use of computer simulation tools for modeling a pilot scale monoclonal antibody production in a Contract Manufacturing Organization (CMO).

To enhance manufacturing efficiency and business competitiveness in the pharmaceutical industry, various design and optimization techniques have been developed in the past decades. Computer-Aided Process Simulation (CAPS) is one such tool that has gained good attention in recent years in improving manufacturing efficiency. It involves the use of computers to perform steady-state heat and mass balancing, as well as sizing and costing calculations for a process.[1] Most often, it enables the identification of missing parameters and predicts the behavior of an integrated process under varying operating conditions. CAPS has been commonly used in the bulk and petrochemical industries since the late 1960s; however, this tool is relatively new to other manufacturing industries. For instance, in biochemical production, the use of CAPS has only been reported since middle 1990s.[2-3] More recently, CAPS also were being used in pharmaceutical production,[4] specialty chemical manufacturing,[5] and food and beverage processing.[6-7]

More recently, the incorporation of economic analysis and debottlenecking functions into CAPS tools enable the process designers to identify economic "hot-spot" of a process at the early conceptual design stage. Various options can then be incorporated and evaluated with CAPS tools to reduce capital and/or operating costs in order to increase production throughput.[8-10]

In this work, a pilot scale monoclonal antibody manufacturing process in a Contract Manufacturing Organization (CMO) is modeled using SuperPro Designer v6.0.11 To increase production throughput, different optimization strategies with alternative process setups are proposed and evaluated. This optimized strategy is next used as an extended base case where uncertainty analysis is carried out with Monte Carlo simulation to quantify risks in meeting targeted plant throughput and profitability.

Base Case Simulation

The production of monoclonal antibody (MAb) from mammalian cell culture is simulated as a base case model with the simulation flowsheet shown in Figure 1. The MAb production consists of upstream (which consists of inoculum preparation and cell culture sections) and downstream processing (consists of recovery and purification sections).

Supporting operations such as media preparation, pre-operation, and post-operation steps, i.e., Cleaning in Place (CIP) and Sterilization in Place (SIP) are also considered in the model. However, buffer preparation is not modeled for simplicity. It is assumed that all buffers, cleaning and storage solutions (apart from that of the automated CIP cycles) are prepared in advance prior to the operation and stored in disposable bags.

The MAb production starts with inoculum preparation in two spinner flasks (in the inoculum preparation section), each of 1 L working volume. Once the desired cell density is

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Figure 1. Simulation flowsheet for the base case model.

achieved, the inoculum is transferred from the spinner flasks to the 5 L bioreactor (00.05.D001). The media solution for spinner flasks is transferred directly from the manufacturers' packaging, while the media solution for 5 L bioreactor is prepared in a stainless steel preparation tank (01.03.T001), together with the media for the subsequent bioreactors (in the cell culture section). The media solution is sterilized by passing through a 0.2 µm sterile filtration unit (01.15.F002/3). Media solution for 5 L bioreactor (00.05.D001) and 30 L bioreactor (02.05.D001) is collected in disposable bags and transported into the designated production area, while media for 200 L bioreactor (02.06.D001) and 1000 L bioreactor (02.07.D001) is transferred directly into the recipient bioreactor via the piping panel.

Upon the completion of the transfer, the media solution is stored in the bioreactors at 4°C until the start of cell culture. Storage at low temperature is made possible by utilizing glycol as the cooling agent. As the 1000 L production bioreactor is operated in fed-batch mode, only 500 L of media solution is transferred at the start of cell culture. Another 300 L of media solution is prepared separately in the preparation tank (01.03.T001) and fed into the bioreactor during the cell culture. The cell culture in the 5 L, 30 L and 200 L bioreactors takes three days each, while the 1000 L bioreactor takes 15 days. The volume of final cell culture broth is approximately 1000 L, containing about 1 kg of MAb.

Upon the completion of the cell culture process, the content of the bioreactors are transferred to the recovery section. Biomass and other suspended compounds (denoted as impurities) in the culture broth are removed using a disposable depth filter system (POD-1). The depth filter area is estimated as 15.4 m² and the filtration rate is set to 38.5 L/min. It is estimated that 5% of the MAb is lost into the solid waste stream during the filtration step. The clarified solution is directed to a stainless steel mobile process vessel (02.23.T001). However, due to its limited capacity, the vessel can only contain 200 L of the clarified solution, while the remaining 800 L is collected in two units

Parameters	02.09.D001	03.09.D001	04.09.D001
Bed height	20 cm	10 cm	20 cm
Bed volume	31.81 L	3.14 L	6.28 L
Resin binding capacity	25 g of product/L of resin	N/A	40 g of product/L of resin
Product recovery yield	90% in 5 BV's of Buffer B	N/A	90% in 5 BV's of Buffer B
Linear velocity	200 cm/h for all operations	200 cm/h for all operations	200 cm/h for all operations
Buffer requirements			
• Equilibration and wash out unbound	13 BV's of Buffer A	13 BV's of Buffer A	13 BV's of Buffer A
• Product elution and column regeneration	10 BV's of Buffer B	10 BV's of Buffer B	10 BV's of Buffer B
• Intermediate column wash	3 BV's of Wash Buffer	N/A	N/A

Table A. Operating parameters for chromatography procedures.

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of 500 L disposable bag. This is followed by 10-fold concentration and five times diafiltration of the clarified solution using a 4.5 m² filtration system (02.16.D001), with filtrate flux set to 140 L/m²h. Retentate of the diafilter is pooled in the mobile process vessel, which is then transferred into disposable bags to be sent to the purification section.

In the purification section, Protein A chromatography is carried out in two cycles using a chromatography system of 45 cm-diameter column (02.09.D001). The operating parameters for Protein A chromatography are given in Table A. The eluant from Protein A chromatography is collected in a 100 L disposable bag and incubated for 45 minutes for virus inactivation. Subsequently, the protein solution is transferred into a 150 L stainless steel process tank (03.23.T001). Tris solution is added into the tank in order to have better pH control for the protein solution. The solution then undergone 5-fold concentration followed by five times diafiltration (03.16.D001; with 1.5 m² filter area and filtrate flux of 140 L/m2.h). The concentrated protein solution from each cycle of Protein A chromatography is pooled in a temperature-controlled disposable bag system (ALG-1).

The next product purification step is flow-through mode anion exchange chromatography (IEX) using a chromatography system with 25 cm-column (03.09.D001). In flow-through mode, it is the impurities that bound to the resin instead of the product. Thus, the product is captured during loading operation and not during elution. The IEX operating parameters are given in Table A.

The protein solution that flowed through the IEX chromatography column is then filtered using a nanofilter for removal of virus residues. This is followed by 5-fold concentration and five times diafiltration of the protein solution using a filter (04.16.D001; with 0.42 m² filter area and filtrate flux of 140 L/m².h). Retentate of ultrafiltration is collected in a 150 L stainless steel process tank (04.23.T001) and transferred into a 20 L disposable bag for polishing step in cation exchange chromatography (CEX).

Polishing step in the CEX is executed in four cycles using a chromatography system with 20 cm-diameter column (04.09.D001). The CEX operating parameters are given in Table A. The eluted solution is collected in the same process tank (04.23.T001) used in the preceding procedure (after cleaning took place). The solution is then concentrated 2-fold and diafiltered five times with product formulation buffer (i.e., PBS), also using the same filtration system (04.16.D001). However, different set of membrane cassettes are used for this procedure. The concentrated protein solution finally passed through a 0.2 µm sterile filter for bioburden reduction prior to bulk filling into an appropriate product container.

In this base case model, different approaches are used to represent the three major chromatography steps; pre-operation, operation and post-operation. This is particularly crucial for chromatography procedures with multiple cycles. Pre-operation and post-operation activities are done only once per batch and not repeated in each chromatography cycle. Thus, the only way to represent these activities is by using a separate unit procedure that uses the same equipment. For instance, procedure P-41 is dedicated for CEX operation that consist of four cycles per batch, while P-41a and P-41b each represents pre-operation and post-operation activities for CEX that are only performed once per batch. Another approach is to use multiple unit procedures to represent the multiple cycles and to include the pre-operation activities in the first cycle and the post-operation activities in the last cycle. This is considerably easy for small number of cycles like in this case; Protein A chromatography that has only two cycles (P-26 and P-31). Otherwise, this approach is rather complicated and may result in a complex flowsheet.

Scheduling Batch Process Modeling

In the modeling framework, scheduling of all operations in each unit procedure is set up based on the setup time,

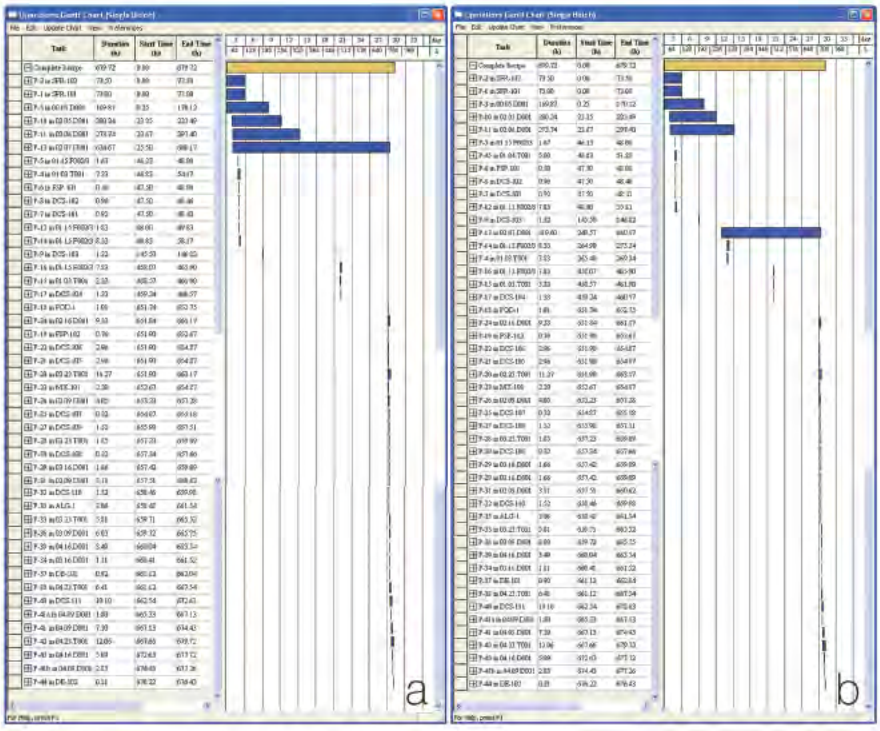

Figure 2. Operation Gantt chart for the base case model.

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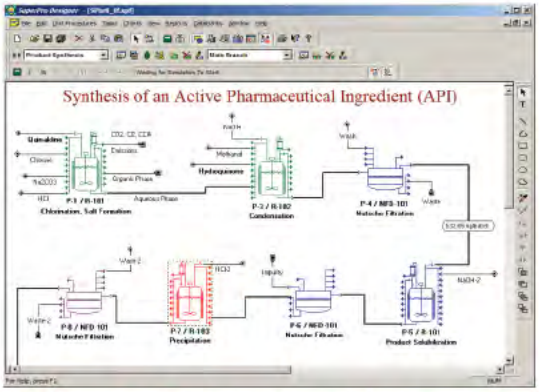

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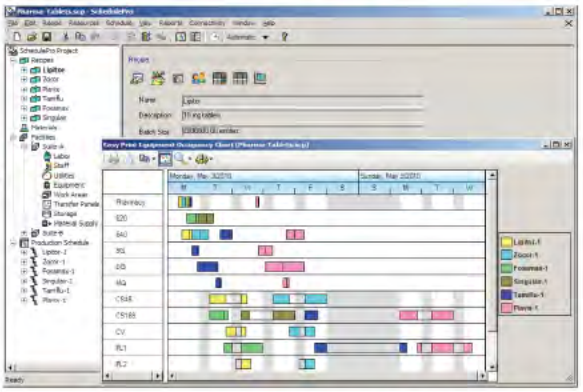

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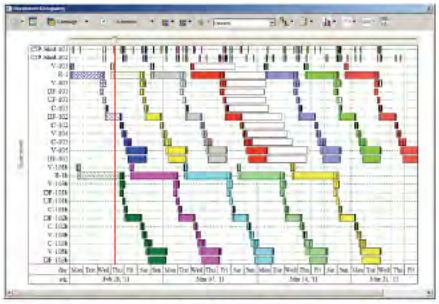

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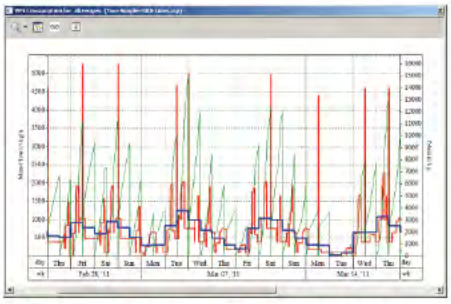
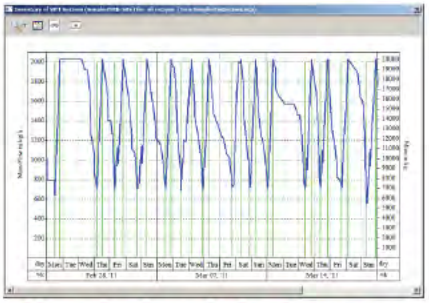


Tracking demand for resources (e.g., labor, materials, utilities, etc.)



Managing inventories for input, intermediate, and output materials

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SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor, utilities, and inventories of materials. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size shared utilities, determine equipment requirements, reduce cycle times, and debottleneck facilities.

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process time, and start time." Setup time is the preparation time required before an operation takes place. This involves equipment preparation or operation setup, such as connection of spool pieces and hoses, as well as the transfer of material from one processing area to another. On the other hand, process time represents the actual processing duration of the operation, whereas start time denotes the beginning of the operation.

Note that process time for certain operations is dependent upon other operations of the same or different procedure. This inter-dependency is represented using the Master-Slave Relationship feature in SuperPro Designer." For example, the transfer in inoculum operation in procedure P-13 is set to follow the duration of transfer out operation in Procedure P-12. In this case, the transfer out operation in Procedure P-12 behaves as the Master operation, while transfer in inoculum operation in procedure P-13 behaves as the slave operation.

In order to accurately represent the process schedule, the start time of certain operations are given a time shift, mainly to avoid overlapping of operations when using the same equipment. For instance, CIP operation in procedure P-24 has a start time shift of 2.50 hours after the previous operation (flushing) ends. This is to allow the completion of CIP 1000L operation in procedure P-13 that uses the same CIP unit. Similar time shift approach is also applied for CIP operations in procedures P-33 and P-38. On the other hand, multiple use of process tank 04.23.T001 for procedures P-38 and P-42, as well as filtration system 04.16.D001 for procedures P-39 and P-43, result in a time shift of 4.5 hours for transfer out operation in procedure P-40. This time shift ensures that sufficient time is allocated to completely clean these two equipment prior to the start of the later procedures. Scheduling of the base case model is represented in the Gantt chart as shown in Figure 2(a).

From the base case simulation model, the plant batch time is determined as 679.72 hours. This is the time required from the preparation of inoculum in the spinner flasks to the final filtration of product in a single batch. A new batch is initiated every 634.67 hours, which corresponds to the minimum cycle time calculated. The 1000 L bioreactor (02.07.D001) of procedure P-13 is identified as the scheduling bottleneck with the longest cycle time (see Gantt chart in Figure 2(a)). On an annual basis, the plant processes a total of 12 batches or a total of 7.62 kg of MAb. For every batch, the MAb recovery yield is determined as 63.5%. In other words, 635 g of MAb is recovered from the 1000 L bioreactor's culture broth.

Table B shows the amount of raw materials required for the MAb production. A large amount of RO water is being used for each batch, primarily for CIP operations. A total

Raw Material	kg/batch	Unit Cost ($/kg)
1X Media Sltn	1,031.50	26.50
CEX Buffer A	324.89	0.27
CEX Buffer B	251.33	0.39
CIP NaOH	6,310.15	0.11
CIP Solution	417.20	0.26
CIP Storage	150.00	0.12
IEX Buffer A	236.21	0.25
IEX Buffer B	31.42	0.58
NaCl (2 M)	139.75	0.85
NaOH (10 M)	232.47	0.20
NaOH (0.25 M)	4.08	0.28
NaOH (0.1 M)	60.00	0.28
NaOH (1 M)	1,700.09	0.35
Oxygen	10,420.80	0.10
PBS	826.53	0.34
ProtA Buffer A	1,341.03	0.29
ProtA Buffer B	636.17	0.45
ProtA Col Sltn	50.00	0.55
ProtA Wash	190.85	0.26
RO Water	12,185.13	0.10
Tris Solution	0.65	5.54
WFI	5,650.12	0.20

Table B. Raw material requirements for base case model (kg/batch).

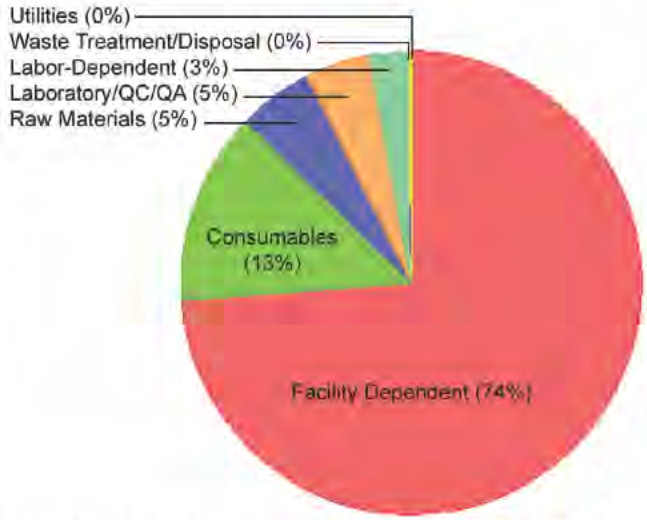

Figure 3. Breakdown of operating cost for the base case model.

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a. Per batch basis					
Test Name	Cost $/Test	No. of Test/Batch			
		Inoculum Preparation	Cell Culture	Recovery	Purification
pH	0.30	11	25	8	65
Conductivity	0.30	2	4	8	65
Cell Count	0.20	9	22	N/A	N/A
Biochemical Analysis	14.80	1	3	N/A	N/A
Sialidase	11.90	9	21	N/A	N/A
Protease	5.30	9	21	N/A	N/A
LDH	5.80	9	1	N/A	N/A
Mycoplasma	39.50	1	4	N/A	N/A
Sterility	10.60	2	4	N/A	N/A
Bioburden	9.00	N/A	N/A	3	32
Endotoxin	52.70	1	4	6	53
TOC	6.10	1	4	3	17
ELISA	26.40	N/A	1	2	9
RP-HPLC	197.40	N/A	N/A	N/A	2
SDS-Page	1.60	N/A	1	2	9
IEF	7.90	N/A	N/A	2	9
BCA	8.70	N/A	1	2	4
Western Blot	13.20	N/A	N/A	N/A	2
Virus Tests	12,650.00	N/A	N/A	N/A	1
Finished Product Test	2,570.00	N/A	N/A	N/A	1
Raw Material	11.00	N/A	4	4	10

b. Annual basis		
Test Name	No. of Test/Year	Cost $/Test
Pre-treated Water	50	19.00
RO Water	350	14.00
WFI	650	66.00
Pure Steam	300	13.00
Environmental Monitoring	2400	4.00

Table C. Laboratory/QA/QC tests for the base case model.

of 5,650 kg WFI is also used for CIP operation (i.e., as final rinse). Apart from the automated CIP operations, all buffers, cleaning and storage solutions are also prepared from WFI. However, the amount of WFI used for the make-up of these buffers and solutions are not shown in the table, but can be calculated from its mass composition, as defined in the stock mixtures databank.

To perform economic analysis of the MAb production, indicative values from the CMO are used. These include the cost of raw materials, consumables, utilities, waste disposals and labor, as well as other economic evaluation parameters, such as depreciation period, income tax rate, etc. A built-in economic evaluation model[4] estimated the total capital cost investment to be $36 million. This estimation is in-line with the CMO's actual capital investment. The plant revenue is calculated based on the production rate of MAb in stream S-208 at a selling price of $1,500/gram. With a unit production cost of approximately $1,000/gram of the purified MAb, the project yields a payback time of 5.18 years with a gross margin of 32.45% and Return On Investment (ROI) of 19.32%. The after-tax Internal Rate of Return (IRR) is 12.27% and the Net Present Value (NPV) is $13 million (based on discount interest of 7%). As an incentive to promote the growth of biotechnology, the CMO is exempted from income tax for the first 10 consecutive years the company derived statutory income from its business. Thus, the income tax rate of the model is set to 0%.

Figure 3 shows the breakdown of the plant annual operating cost. The facility-dependent cost (which accounts for the depreciation of the fixed capital investment, equipment maintenance, insurance, taxes, etc.) is the main contributor, accounting for 74% of the operating cost. Consumables are in the second position with 13% of the total operating cost, which include disposable bags for storage of media and buffers, as well as chromatography resins and membrane filters that need to be replaced on a regular

basis. Raw materials and laboratory/QA/QC components each contributes 5% of the total cost, followed by labor cost at 3%. In this case, the labor cost is set to $5.75 per hour for equipment operation, incorporating factors for fringe benefits, operating supplies cost, supervision cost and administration cost based on the software's built-in model.[11] On the contrary, the labor cost for laboratory/QA/QC work is defined as 15% of the total labor cost for equipment operation and is included in the laboratory/QA/QC cost. The laboratory/QA/QC cost also covers detailed costing of all tests based on the defined frequency and cost per test, either on an annual or per batch basis. Table C provide the sectional lists of laboratory/QA/QC tests considered in the base case model. A section named facility is created in the simulation model to include the annual operating cost in maintaining the facility and utility systems.

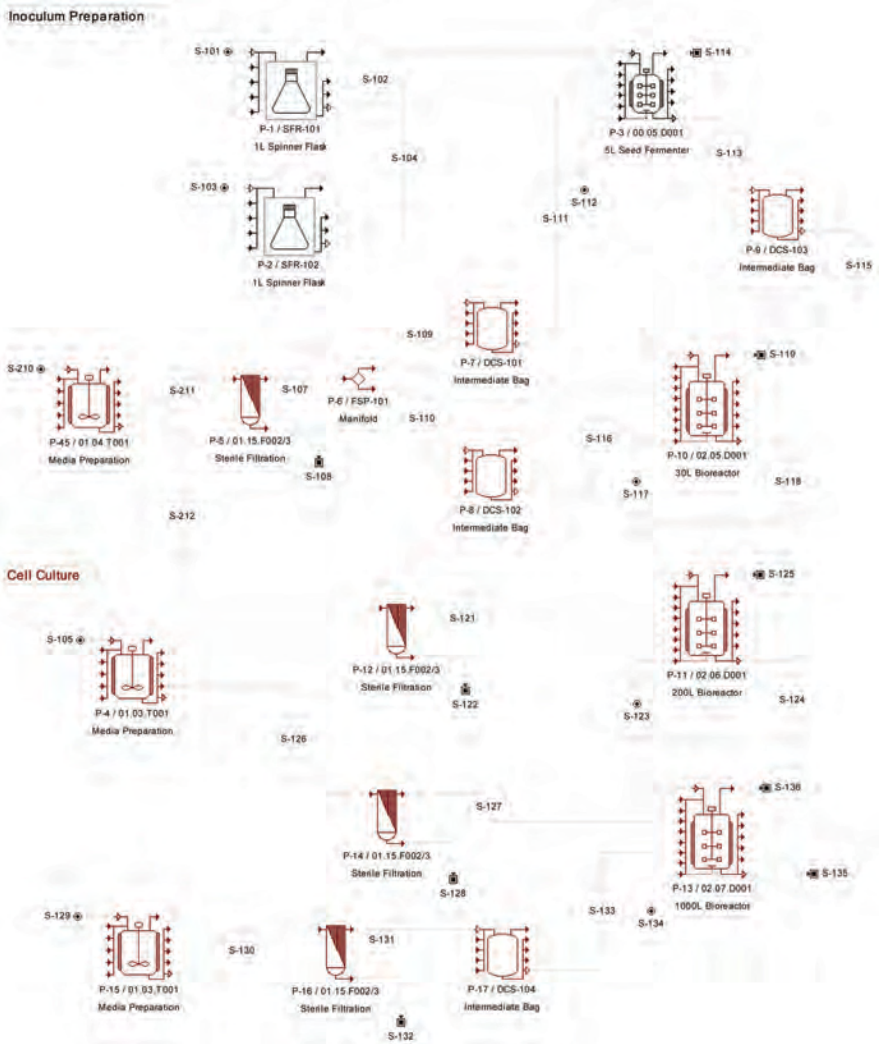

Figure 4. Simulation flowsheet for Optimization Strategy 1.

Optimization Strategies

In order to increase the plant throughput and profitability, two optimization strategies are proposed; however, these are only limited to the existing plant and the equipment housed within it. This is because the CMO has no intention to purchase new equipment due to space constraint in the plant. Apart from the equipment used in the base case model, the following idle equipment, which is designed for the processing of smaller batch size (200 L), may be utilized in the optimized model.

- Stainless steel preparation tank (01.04.T001) of 300 L working volume
- Chromatography column (diameter = 10 cm, height = 50 cm)
- Chromatography column (diameter = 30 cm, height = 50 cm)

Optimization Strategy 1 suggests an alternative setup for media preparation where the idle preparation tank 01.04.T001 is used in addition to preparation tank 01.03.T001. Instead of preparing the media for 5 L, 30 L, 200 L and 1000 L bioreactors in a single tank (01.03.T001), the media is prepared in both 01.03.T001 and 01.04.T001. This setup is illustrated in Figure 4. Preparation tank 01.04.T001 is assigned to prepare the media for 5 L, 30 L and 200 L bioreactors in procedure P-45, while preparation tank 01.03.T001 is dedicated to prepare media for 1000 L bioreactor in procedure P-4 and P-15. As shown in the Gantt chart in Figure 2(b), this strategy reduces the cycle time of the 1000 L bioreactor (02.07.D001 in P-13, time bottleneck for base case) and allows the start of a new batch every 491.60 hours (approximately six days earlier than the base case). This subsequently increases the plant throughput to 18 batches per year. The simulation result indicates that 15.10% increase in operating cost is observed, mainly due to more cleaning operations and the consumption of the 0.2 µm filters in the sterilization of media. Nevertheless, this increase is easily compensated by the significant increase in the number of batches processed per year. Moreover, this alternative setup could reduce the risk of contamination of media in the 1000 L bioreactor, since the media preparation is scheduled just before the transfer of inoculum. This is in contrast with the

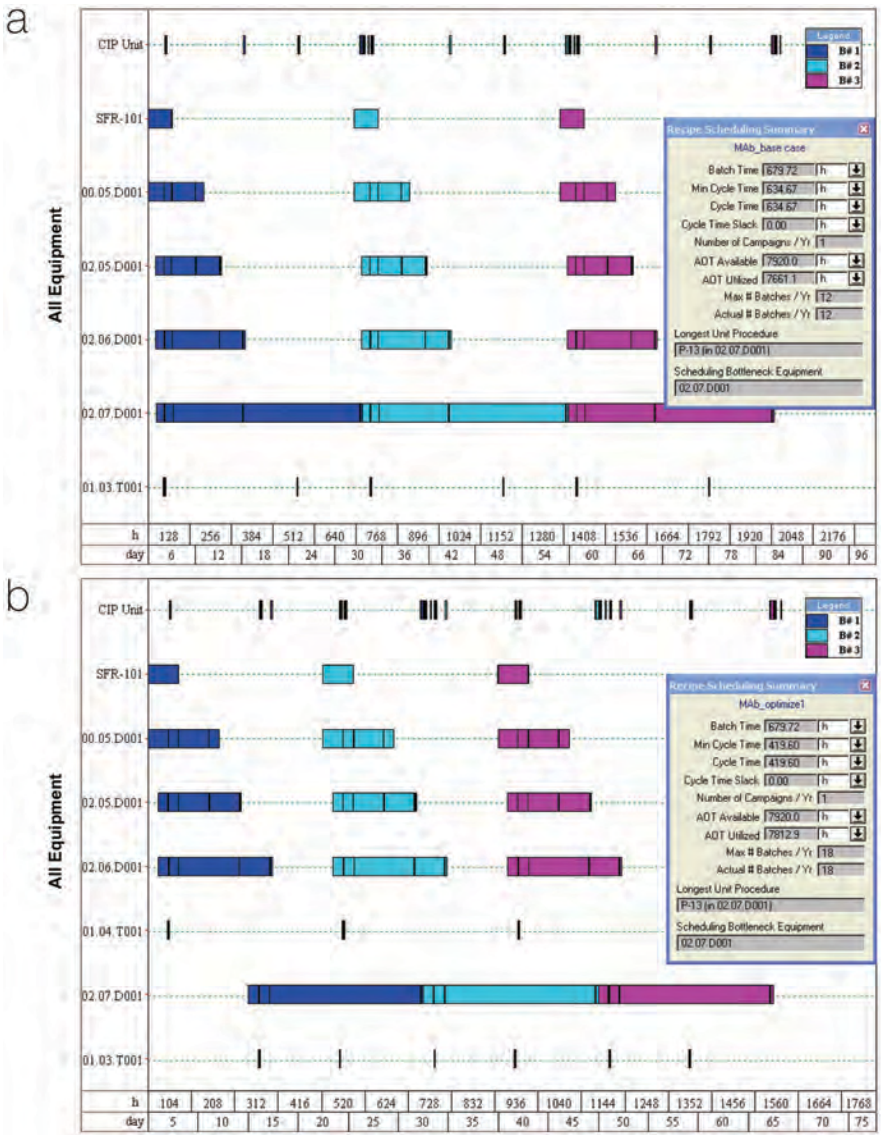

Figure 5. Equipment occupancy chart for (a) base case model; (b) Optimization Strategy 1.

base case model where the media is prepared in advance and stored at 4°C in the bioreactor for about 10 days before the transfer of inoculum. Figure 5 shows the difference in the equipment occupancy for both models and the earlier start of a new batch.

Apart from reducing the minimum cycle time, the process can be further optimized using Strategy 2. In this strategy, the plant operating cost is optimised by reducing the number of cycles for Cation Exchange Chromatography (CEX) in procedure P-41. This is made possible by using a larger column so that more products can be loaded in every cycle. Instead of four cycles in Optimization Strategy 1, procedure P-41 is carried out in only two cycles using a column of 10 cm larger in diameter (while binding capacity remains the same as in earlier cases). The comparison between the procedure setup for Optimization Strategies 1 and 2 is given in Table D. When using a larger column, more chromatography resin is required to pack the column. Nonetheless, the resin is replaced less frequently as a consequence to the less number of cycles per batch. Furthermore, fewer buffers will be consumed for the procedure. These savings are reflected by a 1.04% reduction in the operating cost as compared to Optimization Strategy 1 as seen in Table E.

Table E shows the results of throughput analysis and economic evaluation for the simulation models of the base case, Optimization Strategies 1 and 2. By comparing the economic results, it is apparent that Optimized Strategy 2 with higher ROI and lower payback time would be the best solution to increase the CMO's plant throughput and profitability. This model, henceforth denoted as the extended base case, which are used as the basis for uncertainty analysis, as described in the following section.

Uncertainty Analysis

The simulation model constructed is of deterministic nature. This means that the model will provide reproducible outputs and does not consider the random variation of the inputs. For the simulation models discussed in earlier sections, average value has been used for the varying process input (e.g., cell culture time). In this section, uncertainty analysis is performed on the extended base case model using Monte Carlo simulation. The simulation quantifies the risks in meeting targeted plant throughput and profitability due to uncertainties in opera-

	Optimization Strategy 1	Optimization Strategy 2
Column Diameter (cm)	20	30
Column Height (cm)	50	50
Bed Volume (L)	6.28	14.14
Number of Cycles/Batch	4	2
Cycle Time (h)	1.83	1.82
Total Cycle Time/Batch (h)	7.32	3.64

Table D. Setup of procedure P-41 in Optimization Strategies 1 and 2.

	Base Case	Optimization Strategy 1	Optimization Strategy 2
Batch Time (h)	679.72	679.72	676.38
Minimum Cycle Time (h)	634.67	419.60	419.60
Number of Batches/Year	12	18	18
Operating Cost ($/year)	7,722,008	8,888,431	8,796,397
Production Rate (kg/year)	7.62	11.43	11.43
Unit Production Cost ($/kg)	1,013,316.60	777,744.16	769,691.11
Gross Margin (%)	32.45	48.15	48.69
ROI (%)	19.32	31.12	31.36
Payback Time (year)	5.18	3.21	3.19
IRR (%)	12.27	21.17	21.33
NPV at 7% (%)	12,970,300	42,210,509	42,808,811

Table E. Throughput and economic analyses of the simulation models.

tional parameters and variability in the cost of raw materials and consumables.

Monte Carlo simulation is carried out by integrating SuperPro Designer with an Excel add-in application called Crystal Ball.[11] The probability distributions of the uncertain input parameters for Monte Carlo simulation are defined in Crystal Ball. When running the Crystal Ball application, random values for these parameters are generated using the Monte Carlo method according to their assigned distribution. For each simulation trial, the random values of the uncertain input parameters are sent to SuperPro Designer, which will then perform various calculations for the process flowsheet. This includes material and energy balances, scheduling and capacity utilization calculations, cost estimation and economic evaluation. The values of the output variables from SuperPro Designer are then sent back to Crystal Ball as forecasts. The input and output variables are linked to each other in an Excel spreadsheet using VBA scripts.[11]

Figure 6 shows the flowsheet of the extended base case model, corresponds to the results of Optimization Strategy 2. As mentioned in earlier section, the plant processes a total of 18 batches of MAb per year. The simulation results also determine that the unit production cost is estimated as $770,000/kg MAb. Assuming the company has a production target of 14 successful batches per year, and an upper limit of $900,000/kg of MAb for the unit production cost, the above-mentioned analyses show that the company is able to meet its production and unit cost targets. However, it is beneficial to perform uncertainty analysis to assist the CMO in quantifying the risks of not meeting these targets.

The uncertainty analysis is focused on parameters that may have direct impact on plant throughput (i.e., number of batches per year) and profitability (i.e., unit production cost). The major contributors to the unit production cost are the costs of facility-dependent, consumable, raw material and laboratory/QA/QC. Since production is carried out in an existing plant, variation in facility-dependent cost is negligible. The same assumption goes to laboratory/QA/QC costs, which do not vary much when there are no major changes in the process.

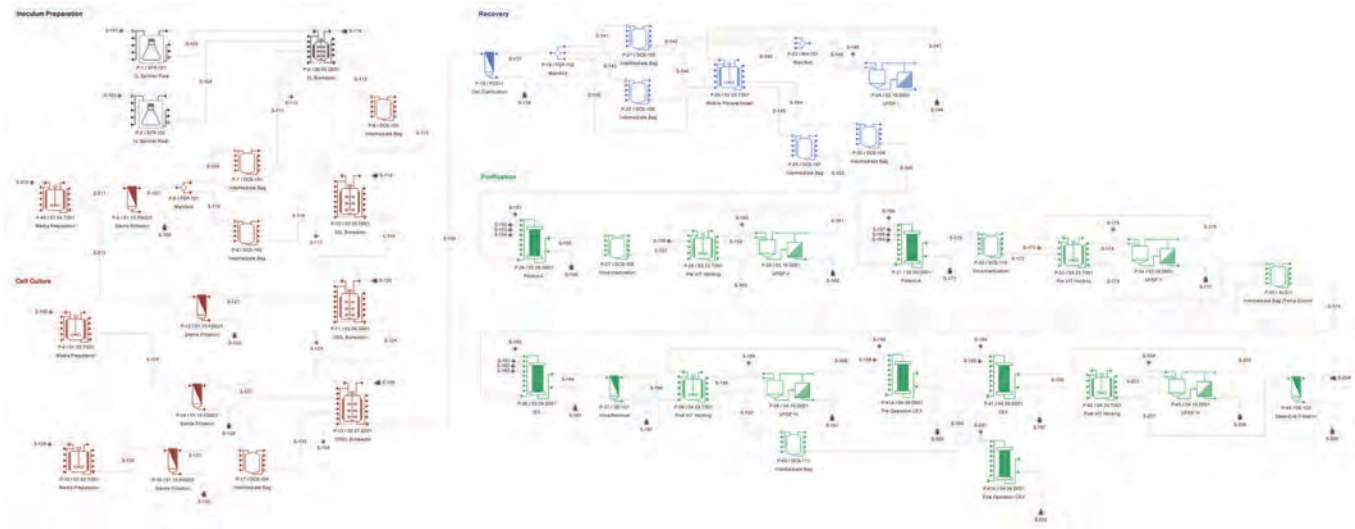

Figure 6. Flowsheet of the extended base case model (Optimization Strategy 2).

Variable	Extended Base Case Value	Distribution	Variation and Range
Cell Culture Time in P-13	15 days	Triangular	[12 - 18]
Cell Culture Time in P-10	3 days	Triangular	[3 - 9]
Cell Culture Time in P- 3	3 days	Triangular	[3 - 7]
1X Media Solution	$ 26.50 /kg	Normal	S.D. = 0.5 [21 - 32]
Protein A Cost	$ 9,405 /L	Normal	S.D. = 2 [8,000 -11,000]
Protein A Replacement Frequency	40 cycles	Triangular	[30 - 50]
Virus Filter Cost	$ 18,500 /item	Normal	S.D. = 6 [17,000 – 19,000]
*S.D. = Standard deviation			

Table F. The input parameters used for the uncertainty analysis and their variation.

Significant uncertainty, however, is expected on the cost of raw materials and consumables as they are highly associated with the supply and demand situation, as well as the world economics. When demand is more than supply, the material price will increase naturally, and vice versa. Furthermore, most raw materials and consumables used in the production at the CMO's site are imported. Fluctuation in world economics will therefore have significant impact on the cost of raw materials and consumables. Detailed analysis shows that 1X Media Solution is the most expensive raw material, which contributes 79.5% of the raw materials cost. On the other hand, Virus Filter is the most expensive consumable, representing about 21.7% of the consumables cost, followed by Protein A at 17.6%.[12]

The plant annual throughput is determined by the minimum cycle time of the scheduling bottleneck (i.e. P-13). Hence, any process change that increase the cycle time of P-13 will result in lower level of annual batch production. In other words, any variability in the completion of P-13 will lead to uncertainty in the plant throughput. This variability is not limited to operations within P-13 alone, but also the variability in the various procedures upstream of P-13. Procedures P-3 and P-10 for example, poses uncertainty in their operations due to the variability in the skills of operators during manual equipment setup (5 L bioreactor and 30 L bioreactor respectively). The worst case would be cell culture contamination in these bioreactors, which will require a complete restart of the entire procedure.

Table F summarizes the input parameters chosen for the uncertainty analysis and their assumed probability distributions. Note that monetary-based variables are assumed to be distributed normally; while time-based variables will follow triangular distribution. The latter is commonly used for continuous distribution with fixed minimum and maximum values. Two forecast variables are considered in the simulation, i.e., the number of batches per year and the unit production cost of the MAb. These variables are chosen based on their significance in production planning and process economics. The output variables of the Monte Carlo simulation are quantified by mean, median, mode, variance, standard deviation, and frequency distribution.

The simulation results (i.e., annual batch production and unit production cost) are presented in frequency distribution curves for the forecast variables. After 1,000 simulation trials, the distribution curves for the forecast variables are normally distributed. The Frequency Chart in Figure 7(a) reveals that the company is able to achieve its production target of minimum 14 successful batches per year with a certainty of 87.20% (represented in blue bars of the curve). On the other hand, the Frequency Chart in Figure 7(b) shows that the certainty of meeting the company's unit production cost target of

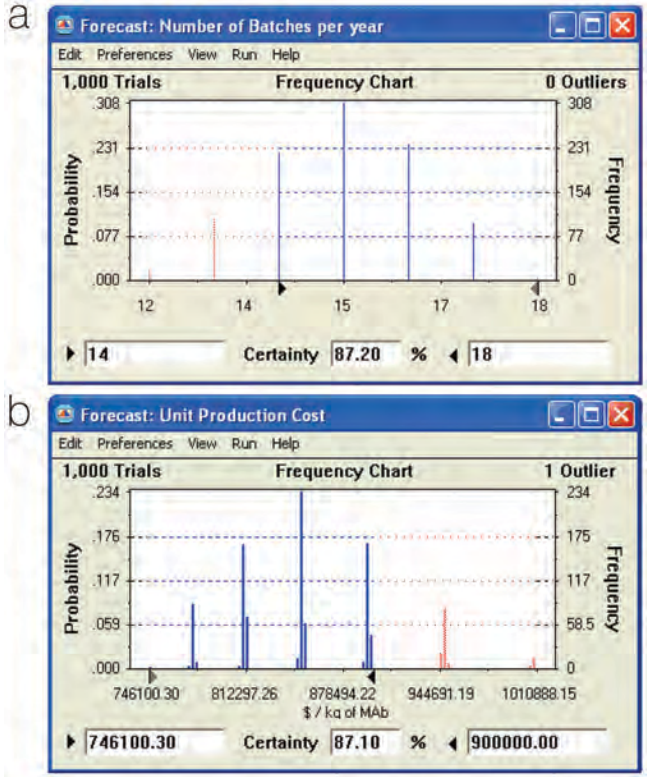

Figure 7. Frequency Chart for (a) annual production; (b) unit production cost of MAb.

$900,000 is 87.10%. Note however that these certainty values are dependence on the input parameters given in Table F.

Apart from Frequency Charts, Sensitivity Charts provide overview on the variation of the forecast variables with respect to the uncertain parameters. This is very useful as it allows the company to identify which input parameter have the greatest impact on the plant throughput and profitability, and thus focus the effort to improve this parameter. The Sensitivity Charts for the annual production and the unit production cost are given in Figure 8. Cell culture time in P-10 (i.e., 30 L bioreactor) has the greatest impact on both the number of batches per year (accounting for 65.4% among the factors), as well as the unit production cost (contributes to 58.6% among the factors). This is followed by cell culture time in P-3 (i.e., 5 L bioreactor). Cell culture time in P-13 (1000 L bioreactor) and 1X Media Solution cost also contribute to the unit production cost, but with much smaller percentage (3.6% and 2.9% respectively). Therefore, the company should focus its improvement efforts on the operation of 5 L and 30 L bioreactor to have a better certainty of meeting its throughput and profitability targets. Better understanding of the process, good process handling, well-trained operators and implementation of advanced automation can help to reduce the variability in the operation of these bioreactors.

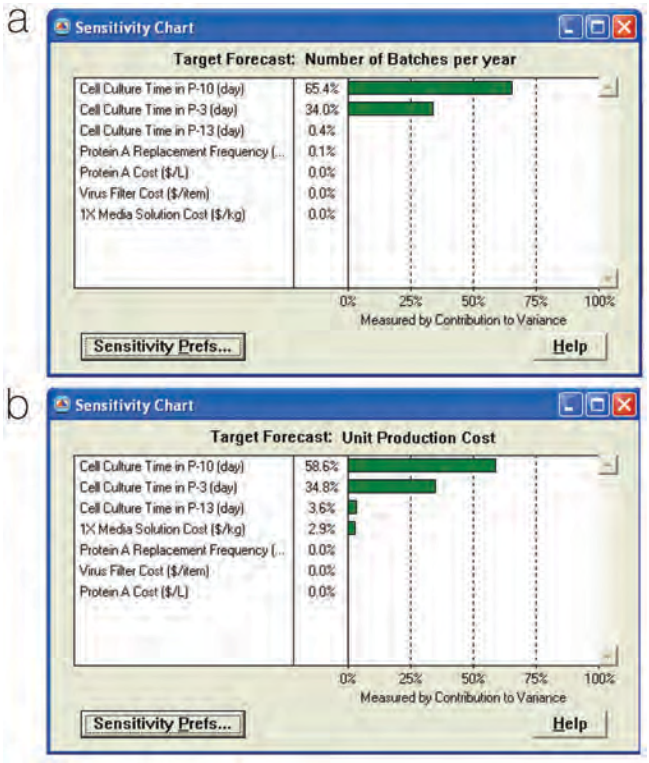

Figure 8. Sensitivity Chart for (a) annual production; (b) unit production cost.

Conclusion

This article demonstrates how CAPS tools are used in modeling and optimizing a pilot scale production of monoclonal antibody. In base case simulation, SuperPro Designer is used to simulate and schedule the production process. Optimization strategies are then proposed and evaluated using the software in order to increase the plant throughput and profitability. Optimization Strategy 2 proves that even without the purchase of new process equipment, the annual throughout of the plant can be increased significantly by reducing the minimum cycle time. This is made possible by using alternative equipment setups and utilizing idle equipment available in the plant.

An uncertainty analysis study is then carried out by integrating SuperPro Designer with a Monte Carlo simulation software known as Crystal Ball. This quantifies the risk in meeting the CMO's target in terms of throughput and profitability. Uncertainties in operating parameters and variability in the cost of raw materials and consumables are taken into account in the simulation. From the analysis, it is determined that cell culture time in the bioreactors have the greatest impact in achieving the targeted plant throughput and profitability.

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Innovations in UV Oxidation Direct Conductivity TOC Measurement to Improve Accuracy and Precision

by Roger Schmid and Randy Turner

This article presents innovations to improve the accuracy and reliability of UV oxidation direct conductivity TOC measurement methods.

Total Organic Carbon or TOC is the carbon whose origin is organic in nature. It can originate from naturally occurring organic acids, such as tannic acid, bacteria, and abrasion of valves. The measurement of TOC is critical to the pharmaceutical industry because various regulatory bodies have established limits for TOC in Water for Injection (WFI) and other uses of water in pharmaceuticals. The main regulatory guidelines are incorporated in the following:

1. USP<643>, "Total Organic Carbon," United States Pharmacopoeia 36-NF 31, U.S. Pharmacopeial Convention Inc., Rockville, Md. (2013).
2. USP<645>, "Water Conductivity," United States Pharmacopoeia 36-NF 31, U.S. Pharmacopeial Convention Inc., Rockville, Md. (2013).
3. USP<1231>, "Water for Pharmaceutical Purposes," United States Pharmacopoeia 36-NF 31, U.S. Pharmacopeial Convention Inc., Rockville, Md. (2013).
4. EP 2.2.38, "Conductivity," European Pharmacopoeia, vol. 7.0, Council of Europe, Strasbourg, France (2013).
5. EP 2.2.44, "Total Organic Carbon in Water for Pharmaceutical Use," European Pharmacopoeia, vol. 7.0, Council of Europe, Strasbourg, France (2013).
6. JP 4.5.2, "Monitoring of TOC as the Indicator for Organic Impurities," JP XVI.

To measure TOC, the organic molecules must be reduced to inorganic carbon allowing quantitative measurement of the resultant carbon dioxide CO2. The organic molecule can be decomposed to inorganic carbon by thermal decomposition, UltraViolet (UV)-persulfate oxidation, and direct UV oxidation. The following are common methods of TOC analysis:

1. Thermal decomposition with NDIR detection
2. UV-persulfate oxidation with NDIR detection
3. UV-persulfate oxidation with conductivity detection
4. Direct UV oxidation with conductivity detection

Each process is based on the oxidation of the organic carbon that is present in the water and the subsequent measurement of the carbon dioxide which results from the oxidation. These methods all have advantages and disadvantages depending on how the oxidation and measurements are technically carried out. Therefore, each application has to be first examined as to which of the different methods is the most suitable.

Methods of TOC Analysis

Thermal Decomposition

With this process, the organic particles are destroyed by high temperatures. In this way, the undissolved components (suspended solids or wear debris) are also completely decomposed - *Figure 1*. This is a common method particularly with a high TOC load (e.g., municipal sewage).

UV-Persulfate Oxidation with NDIR or Conductivity Detection

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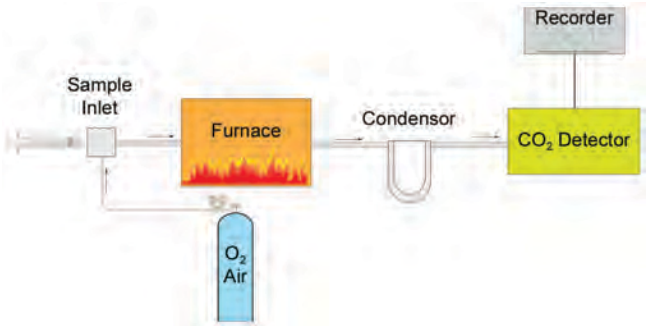

Figure 1. Schematic diagram of thermal decomposition.

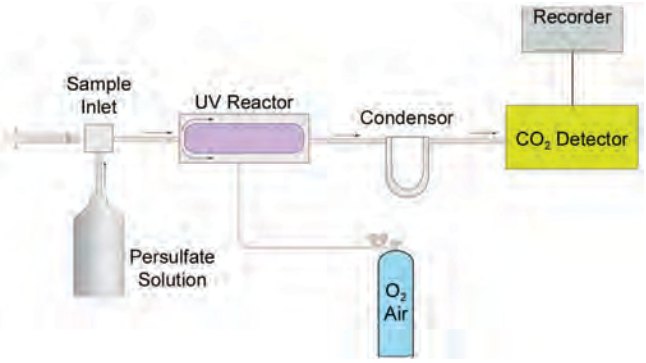

Figure 2. Schematic diagram of UV-persulfate decomposition.

especially with purified water and ultrapure water applications, widely spread and accepted as "the standard." A great advantage of this method is the large operational range of less than 1 part per billion (ppb) to more than 100 parts per million (ppm) with high accuracy.

Direct UV Oxidation

Direct UV oxidation is applied only in ultrapure water and pharmaceutical applications where chemicals are not necessary. These instruments have been increasingly in use over the last few years. This article demonstrates the possibilities and limitations of modern TOC instruments by means of concrete examples. Details of the characteristics of direct UV on-line monitors will be presented to show the latest developments (e.g., functional test) which simplify daily routines and ensure safety. All the above mentioned methods have their particular advantages and disadvantages according to the systems' limitations. For this reason, it is important to choose the instrument exactly for its application and environment.

Direct UV Oxidation with Conductivity Detection

Why is direct UV oxidation often selected to monitor TOC in the pharmaceutical industry? This method is fast and very reliable. Chemicals are not necessary and the maintenance is simple and easy which allows simple and compact analyzers. After the first conductance measurement, the sample flows into the UV-reactor. In this SWAN design, the water is directly channelled over the surface of the UV lamp to the second conductance measurement cell. The TOC concentration is calculated from the different values of the two sensors - *Figure 3*.

TOC = TC – TIC

- **TIC Total Inorganic Carbon**
  The component that originates from inorganic sources, e.g., CO_2
  The values are determined by the first sensor

- **TC Total Carbon**
  The sum of inorganic and organic carbon (TIC plus TOC), the value of which is determined by the second sensor

- **TOC Total Organic Carbon**
  The component that originates from biological sources, e.g., biofilm or cells

TIC in ultra-pure water and pharmaceutical applications is almost solely CO_2 from atmospheric CO_2. In most pharmaceutical production plants, the TIC is greater than the TOC. As with every other system, the direct UV method also has its limitations.

1. Limited range
   a. Conductivity – < 2 microsiemens per centimeter (< 2 µS/cm) at 20°C
   b. TOC – < 1 parts per million (ppm)
2. Reproducibility of UV-oxidation
3. Thermal effects
4. Accuracy

To avoid the mentioned disadvantages, we focused on achieving a complete oxidation by:

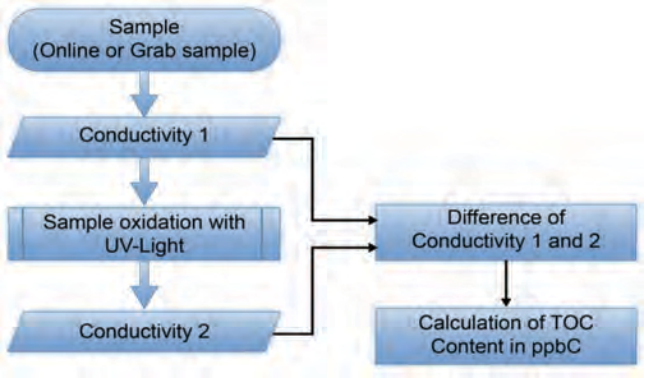

Figure 3. Schematic diagram of direct UV oxidation.

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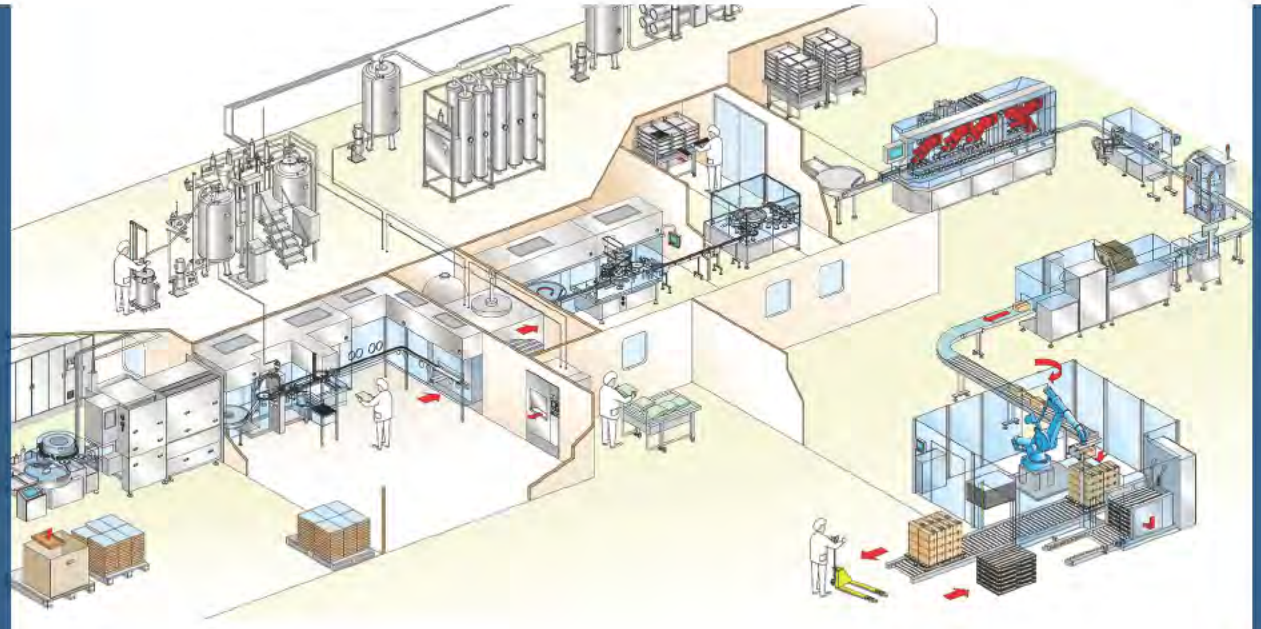

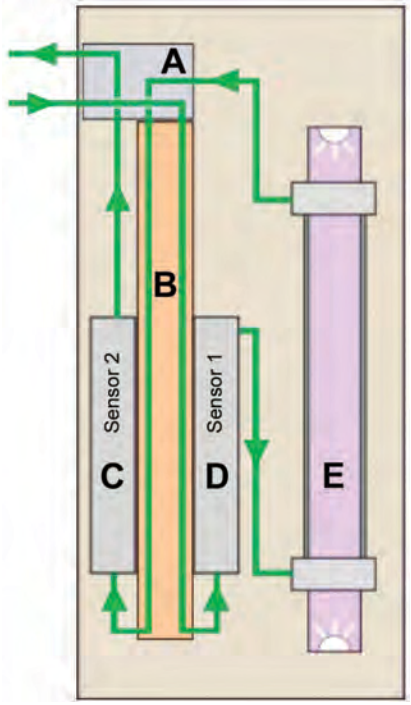

Figure 4. Reactor with a heat exchanger.

1. Stabilization of the thermal conditions
2. Increase of radiation flux
3. Optimization of the sample flow

A few measures and modifications had to be developed to reach this goal. All the presented changes had a huge effect on the method presented below.

Stabilization of the Thermal Conditions

The direct UV-method is strongly influenced by temperature effects. Due to the energy transfer from the UV-lamp, the sample temperature will be increased up to 10°C from conductivity sensor 1 to 2. The conductivity has to be compensated for this temperature difference. Unfortunately, the compensation is only an approximation depending on temperature and conductivity resulting in a potential error in measurement. As a result of our research, the reactor is fitted upstream with a heat exchanger where the outgoing water warms the counter current incoming water. With this, we can minimize the temperature difference between sensor 1 and sensor 2 to below 0.2°C. Particularly, on samples with low TOC values, this modification minimizes measurement errors. The achieved results are considerable stable and have lower variability's than before - *Figure 4.*

Increasing Radiation Density during UV-Oxidation

The UV-lamps (Hg low pressure quartz bulb) employed, have a narrow temperature band where they produce the maximum energy output. This peak point is between 40°C and 50°C. Figure 5 shows the summary spectrum (185 and 254 nm) of an Hg lamp. The 185 nm UV wavelength exhibits a more pronounced impact by temperature.

From the Figure 5, the importance of keeping the temperature of the lamp within the optimal range is clear. Outside influences (environmental temperatures, location) and the sample water itself (changing sample temperatures) can lead to lamp temperatures outside the optimal range.

The heat exchanger solution minimizes the difference between the two conductivity sensors to less than 0.2°C. However, in order to maintain the temperature in the optimal range between 40°C and 50°C, further measures are necessary. An additional heating cartridge or sample cooler as seen in Figure 6 enable a target temperature of 42°C to be precisely sustained. Thus, the maximum radiation efficiency is achieved, resulting in optimal and consistent oxidation.

Optimization of the Sample Flow Through the UV Lamp

The aforementioned measures already show a substantial improvement to the system. The full potential is only

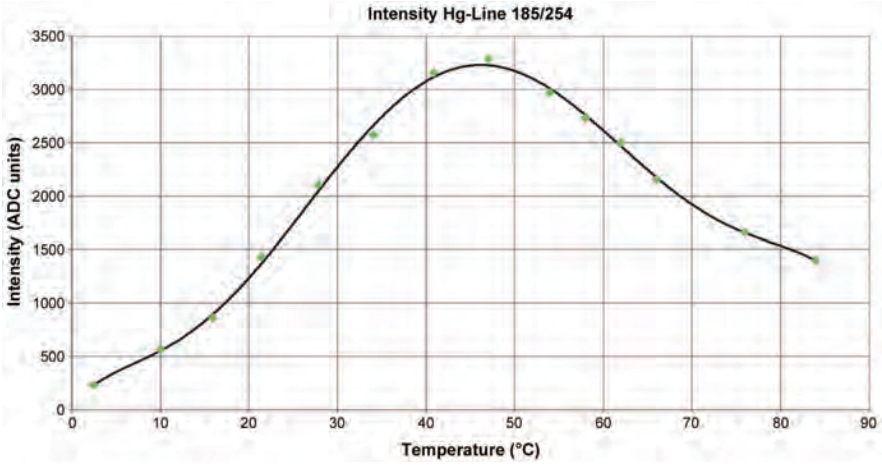

Figure 5. Intensity curve of a mercury low-pressure lamp.

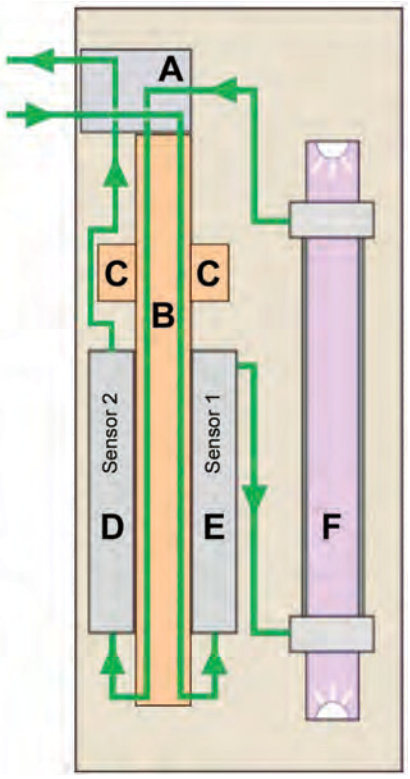

Figure 6. Reactor with heat exchanger and a heating cartridge.

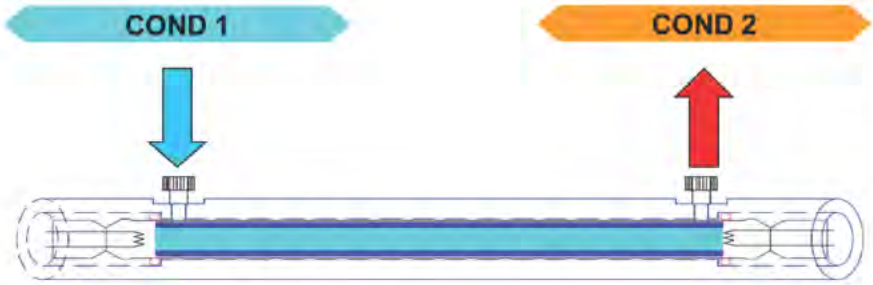

Figure 7. Cross section of a UV reactor.

realized in combination with an optimized sample flow. The classic design of a UV lamp and the sample is flowed around the light source. Divergence loss and reflection are practically unavoidable. The formation of deposits on the directly radiated surface, which decreases radiation density, cannot be fully eliminated in long running operations. This side effect can only be avoided by establishing a direct contact between the UV lamp and the sample.

Figure 7 demonstrates the sample flow in the newly engineered UV reactor. The sample flows directly along the lamp. The furthest distance from the middle of the lamp is 8 mm and the sample layer is only 0.5 mm thick. Divergence loss and ozone production is prevented because of the enclosed construction. This optimization leads to a distinct increase of radiation density, resulting in complete oxidation of the carbon compounds present in the sample. The UV lamp forms a single unit with the reactor case. The entire reactor can be replaced in the case of a failure and is recyclable. Maintenance is easier and faster.

Stable temperatures and a consistent, intense radiation are the foundations for exact and reliable measurement values. Equally important, however, is the compensation method, i.e., how the measured values are converted to the standard temperature.

The Conductivity Measurement

Temperature Compensation

Stable temperature conditions are the basic principles of accurate and reliable test results; however, the compensation method is equally important. This is how the measured conductance is converted to a comparative temperature. The conversion to a common reference temperature can be based on different algorithms; however, these formulas are not absolute. For this reason, SWAN uses two different compen-

sation methods, depending on the chosen application range.

Carbon Dioxide (CO_2) Model

Water for pharmaceutical applications can by definition contain no salt. It can contain traces of organic carbon compounds (TOC) and dissolved carbon dioxide (TIC) from the atmosphere. Atmospheric CO_2 should be the only source of TIC. Below is an actual example with rounded figures:

- Conductivity of the water before oxidation at the first sensor (COND 1) – 0.6 µS/cm at 42°C
- Conductivity of water after UV oxidation at the second sensor (COND 2) – 0.8µS/cm at 42°C
- The absolute conductance of pure water void of CO_2 at 42°C is about – 0.12 µS/cm.

The difference in between the theoretically conductivity of pure water (0.12 µS/cm) and the conductivity at the first sensor (0.6 µS/cm), which in this example is 0.48 µS/cm, must therefore come from CO_2. TIC can be calculated from the definite correlation between conductivity and the carbon dioxide concentration. The corresponding values for the various temperatures are tabulated and stored in the instrument. The organic constituents in our example are converted to CO_2 by the UV lamp resulting in a conductivity of 0.8 µS/cm after oxidation at the second sensor. Consequently, the value at sensor 2 is higher than sensor 1. The difference between the conductivity value at sensor 2 and sensor 1 (due to the oxidation of organic carbon to form CO_2 thereby increasing the conductivity) is converted to ppb TOC an algorithm.

[CONDUCTIVITY 2] – [CONDUCTIVITY 1] = 0.2 µS

Calibration

The calibration is performed with a 1 ppm solution. If the results deviate more than expected from the target value, certain requirements have not been fulfilled, the operating parameters are wrongly adjusted, or the instrument has malfunctioned. This determination of TIC and TOC under the conditions described is an absolute method. The extent of a possible divergence is specified in the menu "installation" and an adjustment cannot be made.

Linear Compensation

This method is meaningful when there is no clear correlation between TOC content and conductivity.

With such applications, a TOC-conductivity (Λ)-model can be constructed by the production of calibration solutions which cover the concentration range of the relevant components. The temperature dependency of the conductivity of the samples only needs to be taken

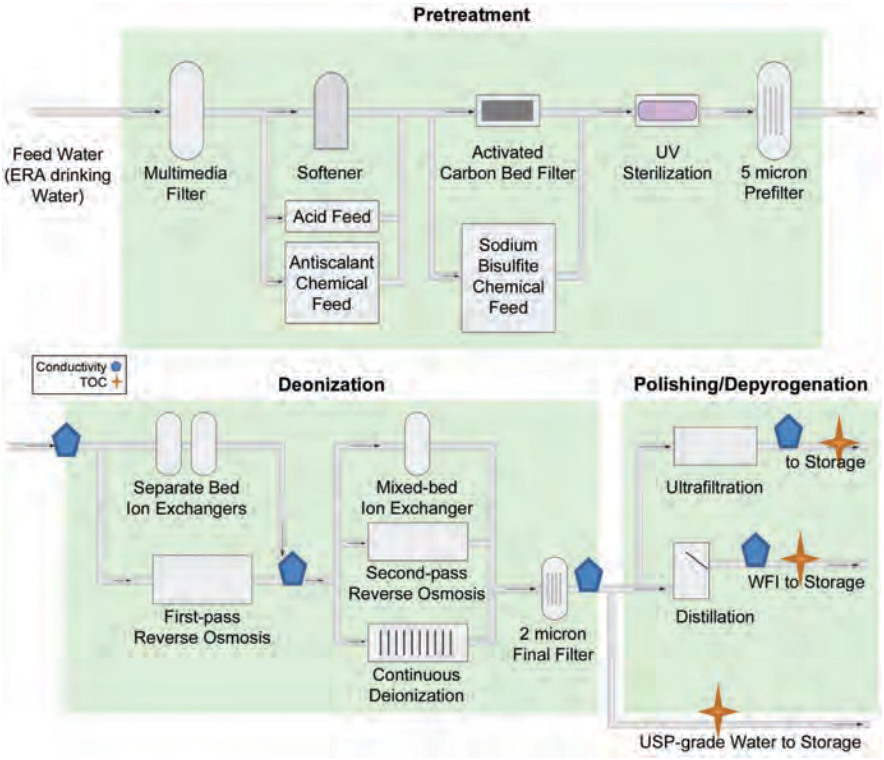

Figure 8. Possible installation in the pharmaceutical water preparations.

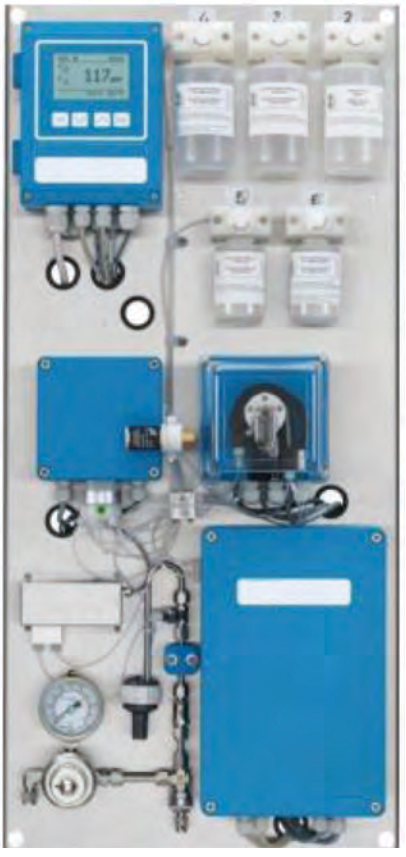

Figure 9. TOC analyzer.

in consideration when the calibration and the online-monitoring are made at different temperatures. The AMI line TOC stabilizes the sample temperature, not just with online-monitoring, but also with a calibration at 42°C to 43°C. In order to allow readings with deviating temperatures, the conductivity values Λ_{in} and Λ_{out} are converted to 25°C.

A constant temperature performance is assumed over the entire measurement range with a linear compensation. This value can be manually changed.

The calibration in linear mode occurs through the measurement of an exactly defined sample solution (Sucrose 1 ppm). Based on the measurement result, the instrument calculates the effective slope, which it displays. From experience, the values are in the range of 0.15 to 0.3.

Pharmaceutical Application

Measurement Points

In modern WFI and Pure Water (PW) plants, most measurements are made at the points mentioned below:

Typically in pharmaceutical plants, it is after the distillation, in the storage tank, at the entrance and exit of the loops and of course at the point of use - *Figure 8*.

The Functional Check – an Aide

Instruments that are installed in pharmaceutical applications must pass a System Suitability Test (SST) according to the authoritative pharmacopeia (USP 643 / EP 2.2.24). The specifications of the test solution in these monographs are described in detail.

If the test is carried out in plants which produce according to the USP guidelines, the solutions have to be produced with USP certified reagents. Due to the extreme dilution, the storage life of these solutions is limited to only a few weeks. An SST is the only possibility to check a TOC instrument in praxis.

The prevailing UV lamps have a life expectancy of six months in instruments with direct UV oxidation. Every lamp exchange requires an SST, which means a minimum of two tests a year. Many operators also use the certified SST solutions more often than the required validation interval, even up to monthly checks. This involves considerable costs and is logistically very time consuming.

The automatic functional test of the AMI line TOC can effectively simplify this routine. The process is similar to the established SST. Highly concentrated solutions (sucrose and benzoquinone) are used, which last up to three months. The solutions are diluted at the time of the test with sample water by an integrated peristaltic pump. Both stock solutions are measured one immediately after the other. Conclusions can be made about the functions and the conditions of the instrument by the degree of recovery. The basic function of the instrument can be easily proved without intervention or external modification. The operator has the ability to examine the instrument regularly online, reducing the number of expensive and elaborate tests.

The functional test is activated manually or by a programmable timer. The applied solutions are not subject to pharmaceutical guidelines and can be produced by the operators themselves. The substances can be purchased from the local chemical distributor as long as they comply with the quality requirements for an analysis.

Simple Grab Sample Testing

An extra benefit of the operating process is the possibility of examining grab samples with the instrument. The sample is drawn through the instrument by a peristaltic pump, regardless of whether it is an SST sample, a functional test or a grab sample - *Figure 9*. Grab samples are easily connected and can be measured immediately by the press of a button. As long as the grab sample measurement mode is active, the signal outpoints of the last value is held to avoid a false alarm.

After the grab sample measurement mode is over, the instrument is rinsed for a set time before the signal points are released to active reporting.

Conclusion

The focus of the development of the TOC analyser concentrated on three areas:

- The stabilizing thermal conditions
- Increasing the radiation density
- Optimizing the sample flow in the system

The technical solutions presented have verifiably improved the precision and accuracy of direct UV oxidation. Moreover, the exacting requirements of the pharmaceutical industry with reference to the standards for calibration and verification were specifically taken into consideration during the development.

Acronyms

PW	Purified Water
TC	Total Carbon
TIC	Total Inorganic Carbon
TOC	Total Organic Carbon
UPW	Ultra-Pure Water
WFI	Water For Injection

Definitions

Adjustment: set of operations carried out on a measuring system so that it provides prescribed indications corresponding to given values of a quantity to be measured.

Note: adjustment of a measuring system should not be confused with calibration, which is a prerequisite for adjustment.

Note: after an adjustment of a measuring system, the measuring system must usually be recalibrated.

Calibration: operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step uses this information to establish a relation for obtaining a measurement result from an indication.

Note: calibration should not be confused with adjustment of a measuring system, often mistakenly called "self-calibration" or with verification of calibration.

Note: often, the first step alone in the above definition is perceived as being calibration.

Validation: the documented act of demonstrating that a procedure, process, and activity will consistently lead to the expected results.

Verification: the process of checking that a product or system meets specifications and that it fulfils its intended purpose.

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Navigating the Regulatory CMC Landscape in China

by Xiling Song, Min Gui, PhD, and Maurice Parlane

This article discusses the challenges and opportunities that multinational pharmaceutical companies (MNCs) have to influence the dynamically evolving regulatory environment in China.

In recent years, China has become not only a manufacturing site attractive to multinational pharmaceutical companies (MNCs) looking to outsource; it also has demonstrated the potential to become an R&D hub, a clinical trial and commercial launch site, and a major market. These changes have made it necessary for MNCs to familiarize themselves with and adapt to the complex regulatory Chemistry, Manufacturing, and Controls (CMC) environment in China, including Chinese requirements for regulatory submissions (Investigational New Drug applications (INDs), New Drug Applications (NDAs), and post-approval changes), the Chinese Pharmacopeia (ChP), and Chinese GMP requirements. Although they face substantial challenges, MNCs have an important opportunity to influence the dynamically evolving regulatory environment in China.

IND Applications in China

For pharmaceutical products that MNCs would like to develop and market in China, it is possible to involve China in simultaneous global clinical trials and submit an IND application to China via a multiregional clinical trial (MRCT) pathway when a Phase 2 study has started outside China.

A major difficulty with IND applications, both for chemical drugs and for biologic drugs, is the lengthy review timeline. Local sample testing is always required for biologic drugs and for chemical drugs for studies only performed in China, which further delays IND approval. Extremely tight review resources in Center for Drug Evaluation (CDE) result in prolonged review timelines, which is not readily improved because of the complexity of the Chinese regulatory system. Creative ways to facilitate faster IND approvals—for instance, rapid approval of INDs already approved in established major markets—are worth considering. In addition, there is no regulatory pathway for submitting CMC changes during development, and this is a critical challenge, especially in the context of new drug development, during which CMC changes are unavoidable.

Recently, progress has been made in the chemical drug submission pathway and review process, including implementation of an annual reporting system through which nonsubstantial CMC changes can be submitted,[1] acceptance of phase-appropriate CMC information, and draft revision of the Drug Registration Regulation, which would permit submission of substantial CMC changes at Phase 1 and Phase 2 development stages.[2] Similar progress is expected for biologic drugs as both the Chinese health authority and domestic industries are gaining knowledge, experience, and confidence in this area.

NDA Applications in China

Involving China in global clinical studies does not mean that a product can be launched as quickly in China as it can in established major markets. The Certificate of Pharmaceutical Product (CPP) is a prerequisite for NDA submission,[3] and this requirement prevents the submission of an NDA in China in parallel with its submission in established major markets, resulting in delayed product launch in China. Lengthy review timelines and local sample testing apply to NDA reviews for both biologic and chemical drugs. Furthermore, evaluation of specifications by the National Institutes for Food and Drug Control (the national sample testing laboratory) during sample testing may be a bottleneck in the NDA review process, especially when ChP requirements can-

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not be met. Relaxation of the requirements for the CPP and for local sample testing would benefit Chinese patients by providing more rapid access to innovative drugs.

Another hurdle, that may jeopardize the supply chain during commercial distribution, is that only one drug product manufacturing site is permitted for each NDA submission. This issue stems from the uniqueness of the Chinese manufacturing site registration system. The China Food and Drug Administration (CFDA) has been striving to revise these requirements, but there has been no progress to date.

Post-Approval Variations in China

The variation guideline from CDE categorizes types of variations.[4] However, it is not clear what information is required to support variations, except for real-time stability data, and the regulatory submission pathway is not specified for each type of variation.

Limited review resources also lead to long post-approval review processes. Sample testing is required for most post-approval applications. Together with the requirement for reference country approval at the time of submission, this leaves the pharmaceutical industry no choice but to plan any post-approval changes in China well in advance. When a change is approved, it must be implemented immediately, per regulation.[4] Industries have been calling for a reasonable grace period to avoid interruptions to the supply chain.

Common Technical Document (CTD) submission is acceptable in China for INDs, NDAs, and post-approval submissions for chemical drugs.[5] CDE started a pilot program in early 2013 to encourage electronic IND submission and the use of a CTD-like template; however, there have been no ensuing announcements or communications regarding detailed requirements.

The Chinese Pharmacopeia

Chinese Pharmacopoeia (ChP) must be compliant at the NDA and post-approval stages.[3,6] ChP has unique requirements, despite the positive trend of increased alignment with ICH 5 guidelines, as indicated by the recent revisions to ChP 2010 and ChP 2012. Up-front awareness of China-specific pharmacopeia requirements mitigates the risk of unnecessary health authority queries during review or the need to take emergency action during inspection due to lack of compliance with ChP. On the other hand, during license renewal applications for legacy products, the CDE may request the applicant to be compliant with the updated USP, Ph. Eur., JP, and BP requirements, although ChP does not contain such requirements.

ChP is currently under revision and open for public comments.[7] The revised version, ChP 2015 (to be implemented on 1 July 2015), will consist of four volumes, including general notices and excipients applicable across all volumes; Traditional Chinese Medicines; Chemical Drugs; and Biologicals and Vaccines. The revision process is expected to be transparent and will be an important opportunity for ChP to move further toward global harmonization.

GMP Requirements

MNCs establishing commercial supply manufacturing in China must comply with the CFDA Good Manufacturing Practice for Drugs, which was introduced in 2010. The regulation comprises 14 chapters, with 313 articles and five annexes covering requirements for the manufacture of sterile products, active pharmaceutical ingredients, biological products, blood products, and traditional Chinese medicines. Draft annexes are being finalized for validation and qualification, computer system validation, and sampling.

Chinese GMP requirements are not harmonized internationally, although China has expressed recent interest in joining the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

MNCs wishing to export from China will be required to gain GMP approval from export markets. Nevertheless, the 2010 GMP represented a significant step toward manufacturing quality commensurate with international expectations.

Official figures released by CFDA in October 2013[8] indicate that of the 1,319 organizations engaged in the manufacture of sterile products, only 429 (32.5%) had achieved the required standard at the time. The regulation requires sterile manufacturers to be compliant by the end of 2013. The same report indicates that of the 3,839 companies manufacturing nonsterile drug products, only 778 (20.3%) meet the new standard. Manufacturers of nonsterile medicines are required to comply by the end of 2015. These data demonstrate the extent of the challenges faced by China and MNCs in implementing and maintaining international GMP standards.

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Induction of Apoptosis by Targeted Ultrasound Contrast Agents in Cancer Therapy

by Lauren J. Jablonowski, Averie M. Palovcak, and Margaret A. Wheatley, PhD

This article presents a proof-of-concept study to determine the ability to target cancer cells through the attachment of a specific ligand to ultrasound contrast agents. It represents the work of a Student Poster Presentation.

According to the American Cancer Society, more than 1.6 million new cancer cases are predicted to have been diagnosed in 2013, with approximately 35% of cases resulting in death.[1] There are numerous challenges associated with treating malignant tumors. Tumors are characterized by high interstitial pressures arising from multiple sources, including aberrant and leaky tumor vasculature, high cell density, unusual composition and structure of the tumor tissue, the composition of the extracellular matrix, and an absence of supporting lymphatic drainage structures.[2-3] In an effort to overcome these challenges, we have previously developed drug-loaded Ultrasound Contrast Agents (UCA) consisting of microbubbles designed to shatter into nanoparticles, or nanoshards (n-Sh), and direct drug-loaded fragments into the tumor interior when insonated with ultrasound (US).[4-8] An advantage of using micron-sized UCA as our platform is that the radiation forces exerted on the UCA by the US beam are expected to propel the UCA toward the leaky pores in the tumor vasculature, and together with the forces associated with UCA collapse caused by inertial cavitation, expel the n-Sh into the tumor for effective therapeutic delivery. This work investigates a new strategy by functionalizing these agents with a targeting ligand that is lethal upon binding to the cancer cell surface receptor. This could be achieved through ligation of **T**umor necrosis factor-**R**elated **A**poptosis-**I**nducing **L**igand (TRAIL) to the UCA surface. The central hypothesis is that US-facilitated *in situ* inertial cavitation of TRAIL-ligated UCA generates functionalized n-Sh displaying tumor-targeting TRAIL. Upon leaving the vasculature and binding to the cancer cell surface receptors, TRAIL will initiate apoptosis in the cell via transmembrane signaling for targeted treatment.

Studies have shown that rapid angiogenesis in established tumors leads to the development of leaky capillaries, with pores measuring from 100 to 780 nm in diameter.[2] Coupled with the lack of lymphatic drainage, tumor-specific vasoactive factors such as vasodilators, nitric oxide and vascular endothelial growth factor promote accumulation of circulating nanoparticles in the tumor interstitium, a process termed the Enhanced Permeability and Retention (EPR) effect.9 Researchers are investigating methods of exploiting EPR for drug therapy.[2,10,11] However, overall reliance on EPR is limited by slow accumulation (up to six hours), inconsistent degrees of vascular permeability between tumor types, and it is precluded entirely in some tumors that do not exhibit an EPR effect.[11-13] As such, numerous studies have focused on developing alternate targeting methods for drug delivery to solid tumors,[3,14,15] and here we explore both ligand-targeting and targeting via focused ultrasound.

Passive targeting of tumors can be augmented by active targeting, which employs receptor-specific ligands. This in turn presents several challenges, including barriers preventing escape of the drug-loaded platform from the vasculature,

sufficient presentation and binding of high affinity ligands to cell-surface receptors, and problems encountered with internalization of the targeted drug.[13] Furthermore, the choice of bioactive species employed to destroy the cancer cells is another critical factor, often involving highly toxic species that can be rendered ineffective by development of Multi-Drug Resistance (MDR). However, specific factors or ligands that trigger apoptosis uniquely in cancer cells circumvent these issues, acting as both a targeting and therapeutic entity. One such ligand is TRAIL, which selectively induces cell death in several groups of cancer cells, but not in healthy cells. Specifically, TRAIL-sensitive cancer cells express death receptors (DR4/TRAIL-R1 and DR5/TRAIL-R2) on their surface, which transmit the transmembrane apoptosis signal to the nucleus for cell death. Healthy cells, however, express decoy receptors (DcR1 and DcR2), which do not transmit this signal, effectively shielding healthy cells from this cancer therapy.[16–22] In clinical trials, TRAIL has performed below expectations, with two possible mechanisms suggested to be the cause.[16,23] First, bioavailability may be diminished due to non-productive binding to the decoy receptors on normal healthy cells. Second, in some cancer cell lines, there are problems with TRAIL resistance, either inherent or acquired, limiting efficacy.[24] Several studies also have investigated methods of overcoming this resistance, identifying compounds such as proteasome inhibitors and other drugs that can potentiate the apoptotic activity of TRAIL.[25–30] In an effort to address the non-specific binding activity of TRAIL, this study investigates the use of tumor site-specific ultrasound-targeting as the primary targeting technique, to be augmented by TRAIL binding to cancer cell surface receptors as in the usually accepted ligand targeting. Death occurs subsequent to, and as a direct consequence of, binding.

Our lab has developed hollow polymeric microspheres, made of polylactic acid (PLA) via a double emulsion process, that are highly echogenic when exposed to US.[7,31–35] These PLA UCA are spherical, approximately 1to 2µm in diameter, and reach approximately 20 dB echogenicity when evaluated in vitro at low concentrations (i.e., 0.03 µg/mL).[7,32,33] It also has been shown that US in the medical imaging range shatters drug-loaded UCA, enabling them to pass through a 400 nm pore size membrane.[4,35] These n-Sh

were measured to have an average size of 350 nm using dynamic light scattering.[4,35,36] As such, these findings suggest that the resulting fragments can be forced through the leaky pores found in angiogenic tumor vessels (< 400 nm pore diameter), especially if the pores are also enlarged by the incident US beam.[37-39] The proposed US-triggered UCA-based delivery mechanism utilizing ligated TRAIL is shown in Figure 1.

The proposed mechanism is that, when exposed to US, the UCA cavitate and burst into n-Sh. This is strongly supported by our experimental evidence.[4,35,36] As shown in Figure 1, UCA pass freely within the vasculature until encountering the ultrasound beam, at which point they **(1)** experience acoustic radiation forces that push the UCA toward the vessel wall. The oscillating pressure wave of the US beam leads to cavitation **(2)** as the UCA gas core expands and contracts in response to changes in pressure. When exposed to sufficiently strong US pulses, the UCA experiences inertial cavitation, resulting in the destruction of the polymer shell (i.e., shattered UCA) **(3)** and *in situ* generation of n-Sh. The energy released in the process of UCA destruction is sufficient to **(4)** enhance the permeability of the vessel wall. The n-Sh then accumulate within the tumor interstitium **(5)** due to production of microjets and shear forces created when the microbubbles collapse due to inertial cavitation propelling the fragments through the vessel wall and into solid tumor tissue. There, **(6)** the ligated TRAIL can bind to cell surface receptors and signal for apoptosis, while the n-Sh degrade.

UCA could be further modified to co-encapsulate bioactive molecules within the polymer shell, which would undergo sustained localized release as the n-Sh degrade, providing a mechanism for delivery of agents to overcome resistance.

This work describes the development of UCA coated with the targeting ligand TRAIL. These agents have the potential to generate TRAIL-ligated n-Sh at a tumor site, targeting the death cell receptors to initiate apoptosis. If successful, these UCA represent an agent capable of overcoming many of the obstacles in current chemotherapeutic methods, including reduced bioavailability, systemic toxicity, and MDR, therefore better serving the population with solid malignant tumors.

Methods

Ultrasound Contrast Agent (UCA) Preparation

UCA were prepared using the water/oil/water (w/o/w) emulsion process that has been well-established previously.[7] Briefly, 10 mL of methylene chloride, 0.05 g camphor, and 0.5 g PLA (100 DL 7E, Evonik, (Birmingham, AL) were added to a 50 mL beaker, and stirred for 15 minutes to ensure that all of the polymer has dissolved. Then, 1 mL of 0.4 M ammonium carbamate solution was added to the organic phase and sonicated (Misonix XL2020) on ice for 30 seconds, with 1 second pauses between 3 second pulses. The first emulsion was then added to 50 mL of 5% poly(vinyl alcohol) (PVA) (25kDa, 88% mol hydrolyzed) solution kept at 4°C, and homogenized (Brinkman PT 3100 Polytron) at 9500 rpm for 5 minutes to create the second emulsion. After homogenizing,

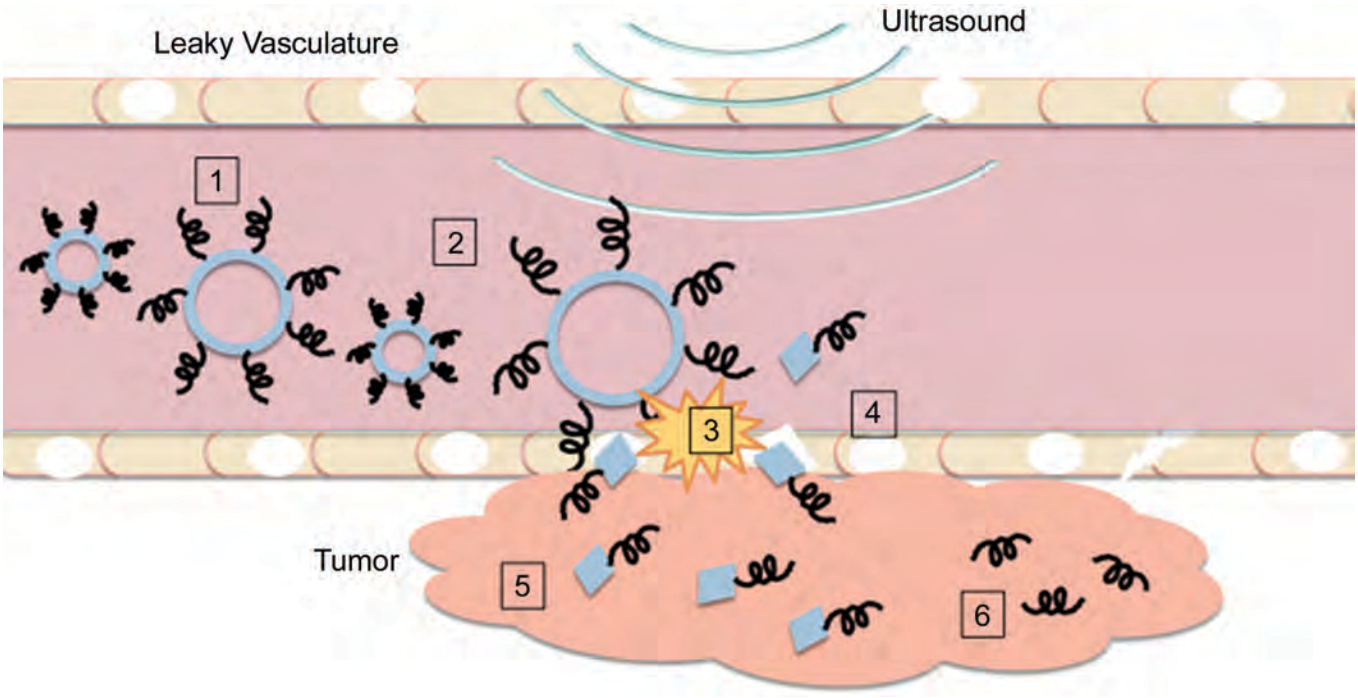

Figure 1. Schematic of ultrasound-triggered delivery using polymeric contrast agents. Blue circles represent UCA, yellow starburst indicates US-triggered UCA collapse, and black lines represent functionalizing ligands (not to scale). Refer to text for identification of numbers (1-6).

100 mL of 2% isopropanol was added, and the solution stirred at 375 rpm for 90 minutes at room temperature to evaporate off the organic material. The remaining UCA solution was centrifuged at 5000 rpm for 5 minutes, and the pellet was collected and washed three times with hexane to remove any remaining organic material. After drying for 20 minutes, the UCA were washed with distilled water, centrifuged, and the pellet was flash frozen in liquid nitrogen and then kept frozen at -80°C for at least 2 hours. The frozen UCA solution was then lyophilized for 48 hours to remove the aqueous core material, thus resulting in the formation of air-filled hollow microcapsules.

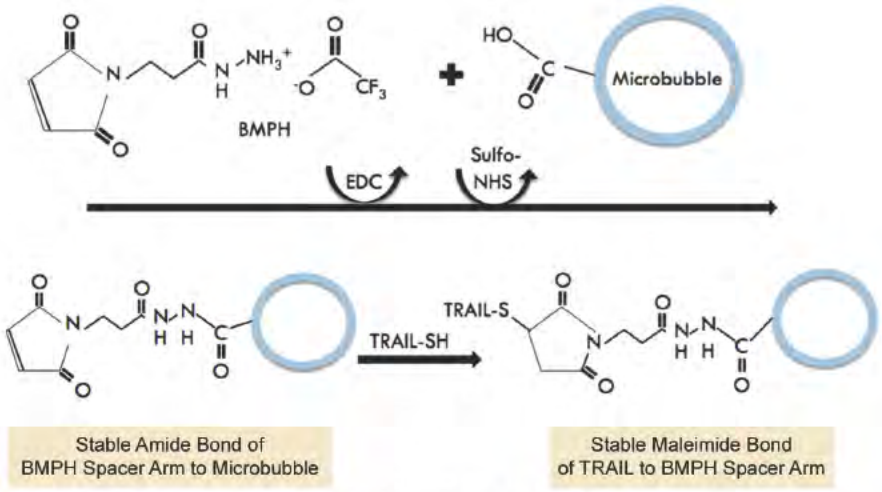

Figure 2. Maleimide reaction to bind TRAIL to the UCA surface.

Functionalization of UCA with Targeting Ligand

Once the microbubbles were formed, TRAIL (Sigma-Aldrich, St. Louis, MO) was ligated to the UCA surface using a maleimide reaction[40-41] with an N-beta-Maleimidopropionic acid hydrazide (BMPH) (Fisher Scientific, Pittsburgh, PA) spacer arm of 0.81 nm in length, using N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) and n-hydrosulfosuccinimide (NHS), both from Sigma-Aldrich (St. Louis, MO) to activate and catalyze the reactions as seen in Figure 2.

Briefly, 60 mg of UCA were suspended in 4 mL of 0.1 M

2-(*N*-morpholino)ethanesulfonic acid (MES) buffer (pH 5.2) (Fisher Scientific, Pittsburgh, PA), while the solutions for cross-linking were prepared (14.86 mg BMPH in 1 mL distilled water (dH_2O), 19.17 mg EDC in 1 mL dH_2O, and 12 mg NHS in 1 mL dH_2O). These solutions were added to the UCA suspension, which was then shaken end over end for 30 minutes. Activated UCA were then centrifuged at 5000 rpm (relative centrifugal force 2599.35 g) for 5 minutes and washed to remove unreacted EDC, resuspended in a solution of 1.2 µg TRAIL in 4 mL phosphate buffered saline (PBS), and shaken end over end for 90 minutes. TRAIL-ligated UCA (TRAIL-UCA) were then centrifuged (5000 rpm for 5 minutes), washed 3 times with dH_2O, flash frozen in liquid nitrogen, and lyophilized for 48 hours. In addition to unmodified control UCA, an additional control group was created following the ligation procedure, but without the use of chemical cross-linkers EDC and BMPH (non-linker control), to account for the possibility that observed effects were from TRAIL that was only adsorbed to the surface rather than covalently linked. Such adsorbed TRAIL would be easily eluted when contacted with cell cultures, releasing free TRAIL.

Physical and Acoustic Characterization of UCA

Ligated and control groups were morphologically and acoustically evaluated to determine their viability as functionalized UCA. Scanning Electron Microscope (SEM) images were taken with a Philips FEI XL30 Environmental SEM to assess the UCA surface morphology and ensure that the size had not changed substantially during the ligation step. Briefly, 1 mg of UCA was mounted onto an aluminum stub using conductive adhesive tape and sputter coated with platinum-palladium for 40 seconds to prepare for SEM imaging. Three images are taken from a random location on each SEM stub holding the microbubble sample. UCA diameter was measured from these SEM images, using NIH ImageJ image processing software. Briefly, four microbubbles were chosen at random by the researchers from these representative images, the diameters of these microbubbles were measured with ImageJ software, and the results were average for each UCA species. Dose and time response tests were performed in a custom-built acoustic testing system in our lab, using a 5 MHz, 12.7 mm diameter, single element ultrasound transducer (Panametrics, Waltham, MA) spherically focused at a length of 50.8 mm, as described previously.[5-7,32,34] This transducer was submerged in a bath of distilled water warmed to 37°C and focused through the acoustic window of the custom-built sample vessel filled with 50 mL of warmed (37°C) PBS. A Panametrics Pulser/Receiver was used to insonate the sample at a pulse repetition frequency (PRF) of 100 Hz. The reflected signals were then received and amplified by 40 dB, fed to a digital oscilloscope (LeCroy, Chestnut Ridge, NY), and analyzed on a computer using a custom LabView program. Baseline readings were taken of the PBS alone, while spinning with a magnetic stir bar, to indicate the amount of background for sample measurements. Then, 3 mg of UCA were suspended in 800 µL of PBS for testing. To determine the cumulative dose response, 20 µL of the UCA suspension were added to the sample vessel every 30 seconds and the acoustic signal was measured at each time point. Time response, or stability over time while circulating in the US beam, was measured by adding 40 µL of the UCA suspension to the sample vessel with a fresh 50 mL of warmed PBS and the acoustic signal was measured every minute over a period of 15 minutes. These tests were done in triplicate, and the results reported as the average of these readings.

In Vitro Ultrasound-Triggered Nanoshard Generation from UCA

After demonstrating the potential to produce US-triggered n-Sh with the TRAIL-UCA during acoustic tests, UCA were insonated using methods that have been used previously in our lab to generate n-Sh.[4,36] Briefly, sterile 6-well polystyrene tissue culture plates were clamped at the water-air interface of the acoustic tank described above. The submersible transducer was re-positioned to transmit upward into the wells of the plate, at a distance such that the focal point was within the well. Polyester Transwell membrane inserts (Corning, Lowell, MA) with 400 nm pores (pore density 4×10^6 pores/cm^2, diameter 24 mm) were inserted into the wells to simulate the leaky vasculature. 5mg of TRAIL-UCA were suspended in 3 mL of PBS in the bottom of the well, then the Transwell was inserted, and an additional 3mL of PBS was added on top of the insert. The well was then centered over the transducer at a distance of 50.8 mm (the focal distance of the transducer), and a rubber stopper was placed at the upper level of the fluid in an effort to minimize energy reflection at the liquid-air interface and to prevent standing waves from forming within the sample. The sample was then insonated at a PRF of 100 Hz for 30 minutes, taking 200 µL samples from the upper chamber every 10 minutes for experimental use. Controls were incubated in this setup for 30 min, without insonation.

In Vitro Characterization of Ligated UCA Ability to Induce Cell Death

Finally, *in vitro* studies assess the targeted apoptotic activity

Negative Controls	Positive Controls	Test Group 1	Test Group 2
No Treatment	Free TRAIL	Intact Non-linker UCA	Intact TRAIL-ligated UCA
Intact Blank UCA		Non-linker n-Sh (30 mins insonation)	TRAIL-ligated n-Sh (30 mins insonation)

Table A. Treatment groups for *in vitro* cell studies, both TRAIL-sensitive and TRAIL-resistant cell lines.

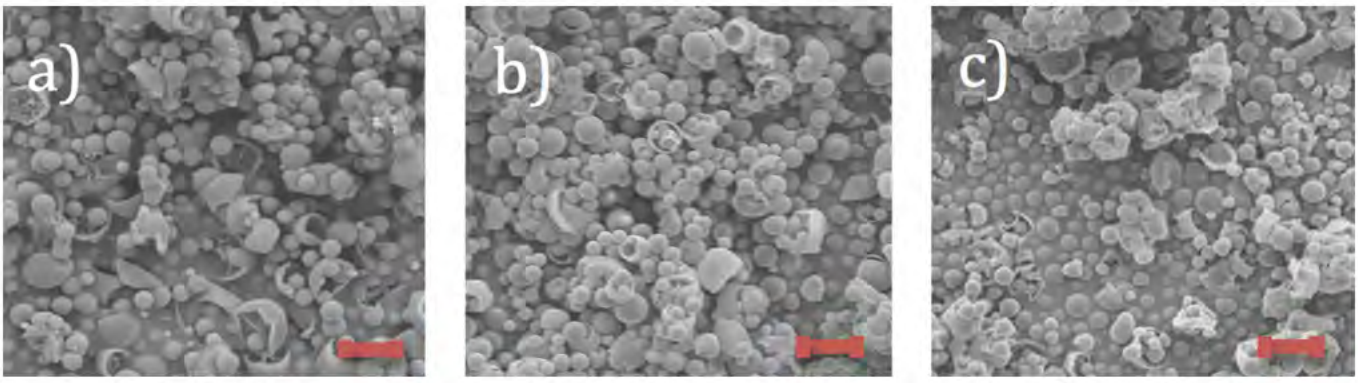

Figure 3. SEM images of UCA. a) Pre-ligation blank UCA. b) Ligated TRAIL-UCA. c) Non-linker control TRAIL-UCA. Accelerating voltage 5 kV, spot size 3, magnification 2500×, scale bar 4 µm.

induced by the TRAIL-UCA and TRAIL n-Sh. The "supernatant" from the n-Sh tests described above was collected, centrifuged, and then suspended in cell culture media. MDA-MB-231 breast cancer cells were grown to 80% confluence in 48-well plates (to facilitate multiple treatments) in media containing 94% RPMI 1640, 5% FBS, and 1% penicillin/streptomycin antibiotic; 3T3 fibroblasts, representing a TRAIL-resistant group, were grown to 30% confluence based on availability.

Individual batches of both cell types were exposed to seven different treatments representing each treatment vehicle and controls, shown in Table A. Cells were incubated in media containing each treatment for 6 hours, and cell fates were then evaluated using a Live/Dead Cytotoxicity Assay (Invitrogen, Grand Island, NY) and fluorescent microscopy. Images were taken at three random positions throughout each well, and can be considered representative images. Cell fates were counted using customized macros in NIH ImageJ. Briefly, all cells in the image were counted and designated as either live (green) or dead (red). Then, cell death was calculated by determining the percentage of dead cells compared to live cells in these representative images.

Statistical Analysis

Statistical analysis is performed using GraphPad Prism software, where one-way ANOVA analysis is used to determine significance (95% confidence level) and student's t tests are used for individual group comparisons. Error bars represent the Standard Error About the Mean (SEAM).

Results

Physical and Acoustic Characterization of UCA

The resulting TRAIL-UCA and unmodified blank UCA were characterized by evaluating surface morphology before and after modification, as well as acoustic enhancement and stability in the US beam. As shown in Figure 3, SEM images

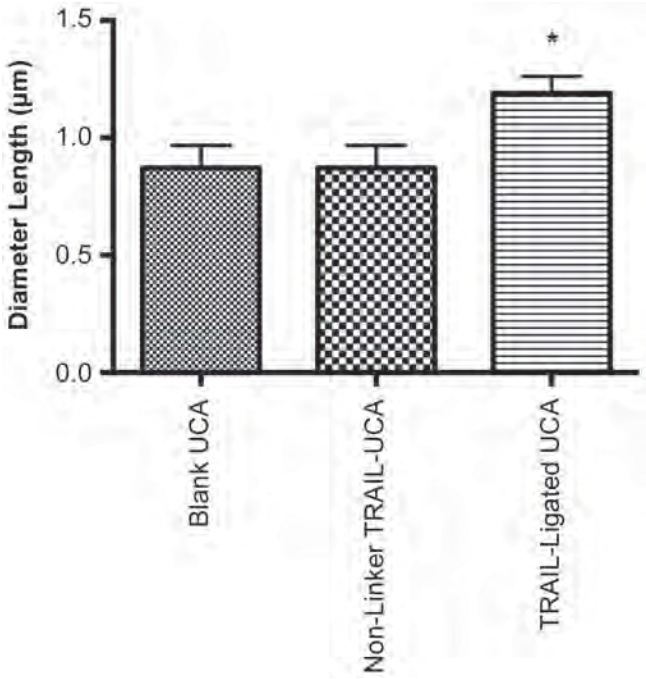

Figure 4. Average UCA diameter, as measured from SEM images. * p=0.0153.

demonstrate that TRAIL attachment does not significantly affect surface morphology as pre- and post-ligation images show smooth, spherical UCA.

Additionally, these SEM images were used to measure UCA diameter, and the results are shown in Figure 4. While the average diameter of blank UCA (0.871 ± 0.097µm) and non-linker TRAIL-UCA (0.871 ± 0.097µm) were identical, the SEM images indicate a shift in the size distributions for the non-linker controls. The average diameter of TRAIL-ligated UCA (1.190 ± 0.072µm) was significantly larger than these controls ($p = 0.0153$). These changes in size can be expected, due to structural modifications being made to the UCA shell during the ligation process. Nonetheless, these agents are within the desired 1 – 2 µm range for average diameter, and are therefore acceptable for these experiments.

To assess whether the agents retained their function as contrast agents, acoustic enhancement and stability were assessed. The cumulative dose response results are shown in Figure 5a, where a 5-8 decibel (dB) reduction in maximum enhancement at a value of 12 µg/mL is seen in the TRAIL-UCA groups when compared to blank PLA controls at the same dose, suggesting that UCA shell properties are altered during maleimide attachment of TRAIL. Despite this modification-induced reduction, both test groups were still able to reflect a clinically-relevant US signal as judged by our previous *in vivo* work,[32] suggesting that TRAIL-UCA are still effective contrast agents. In fact, Figure 5b suggests that the process of TRAIL ligation may actually enhance acoustically-triggered n-Sh production, since the stability in the US beam is reduced for these groups compared to the blank PLA control. The acoustic half-life, or time until the enhancement signal is halved, is assumed to be due to UCA rupture. For comparison, this half-life was approximately 9 minutes for the ligated TRAIL-UCA and approximately 12 minutes for the surface adsorbed TRAIL-UCA, whereas the half-life of the control blank UCA is greater than 15 minutes. However, there is not a large enough difference between the ligated UCA and non-linker controls ($p > 0.05$) to suggest that the ligation itself has a large effect on the UCA shell properties. Overall, these results suggest that the aqueous environment to which the UCA are exposed during TRAIL attachment modifies the UCA structure, as the SEM images showed no visible change in morphology. The results also indicate that the agents are still capable of functioning as contrast agents that shatter when exposed to US. The larger dose that is required to reach maximum enhancement for

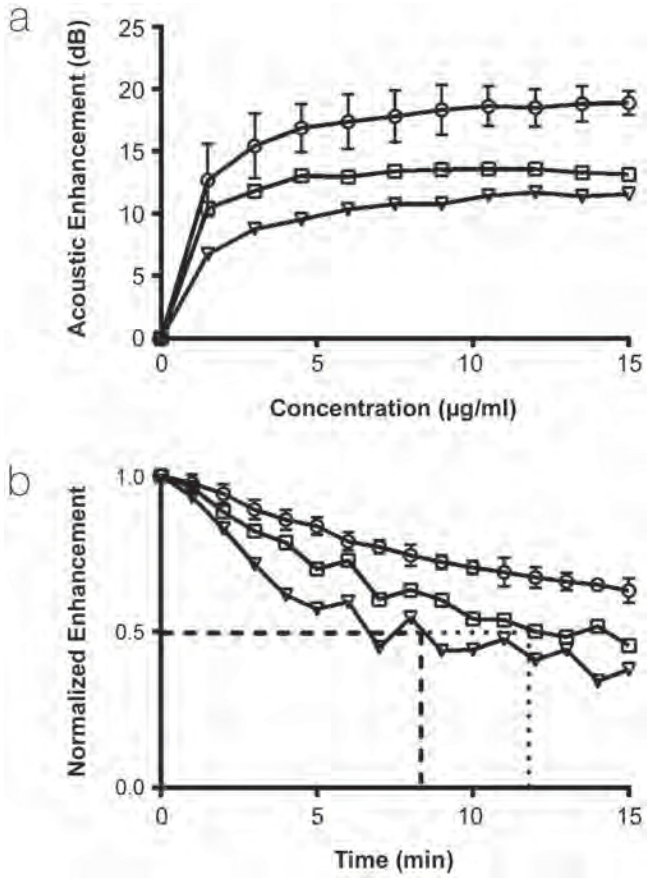

Figure 5. Acoustic evaluation of UCA. a) Acoustic enhancement of each agent, 15 µg/ml doses added and read every 30 seconds, with cumulative enhancement reported in dB. b) Acoustic stability of each agent, normalized to 1, with readings taken every minute, dotted lines indicate half-life of agent. ○ Blank PLA (n = 3), □ Non-linker TRAIL-UCA (n = 1), ▽ Ligated TRAIL-UCA (n = 1).

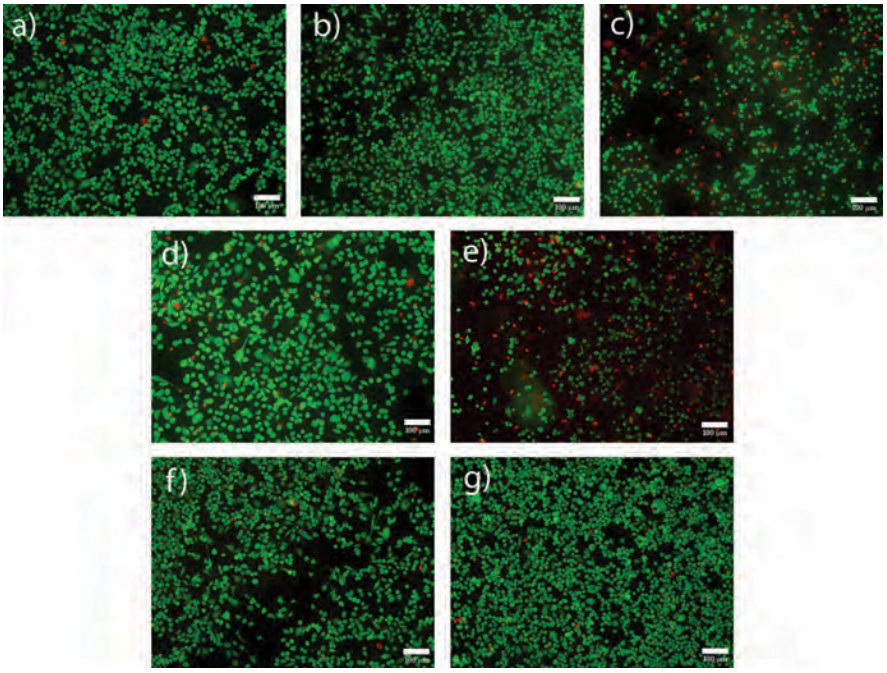

Figure 6. Fluorescent images of MDA-MB-231 human breast cancer cells under various treatments. Green indicates live cells, red indicates dead/apoptotic cells, scale bar 100µm. a) no treatment (negative control), b) intact blank PLA UCA (negative control), c) free TRAIL (positive control), d) intact ligated TRAIL-UCA, e) ligated n-Sh, g) intact non-linker TRAIL-UCA, and g) non-linker n-Sh.

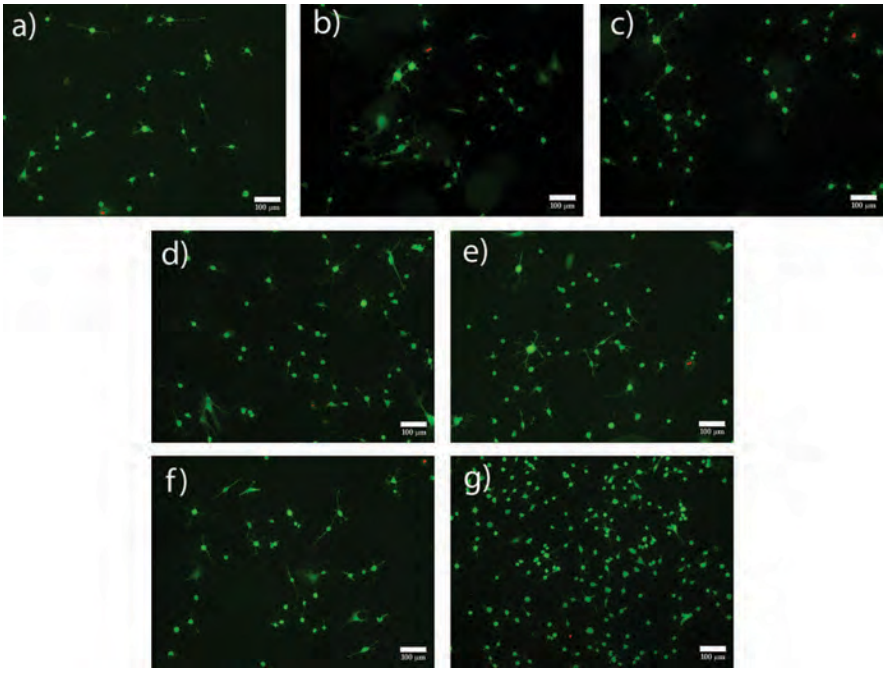

Figure 7. Fluorescent images of 3T3 human fibroblasts under various treatments. Green indicates live cells, red indicates dead/apoptotic cells, scale bar 100µm. a) no treatment (negative control, 1.742 ± 0.076% cell death), b) intact blank PLA UCA (negative control, 2.548 ± 0.016%), c) free TRAIL (positive control, 1.669 ± 0.056%), d) intact ligated TRAIL-UCA (2.753 ± .051%), e) ligated n-Sh (0.799 ± 0.041%), f) intact non-linker TRAIL-UCA (1.106 ± 0.031%), and g) non-linker n-Sh (0.659 ± 0.267%).

TRAIL-UCA is probably due to the fact that a portion of the UCA are destroyed during the ligation process, resulting in a lower concentration of intact UCA.

In Vitro Characterization of Ligated UCA Ability to Induce Cell Death

In the test groups, cells were treated with modified cell culture media consisting of the appropriate intact UCA or n-Sh population suspended in the medium. The treatment groups were: intact non-linker TRAIL-UCA, non-linker n-Sh after 30 minutes of insonation, intact ligated TRAIL-UCA, and ligated n-Sh after 30 minutes of insonation. The control groups were: no treatment (negative control), intact blank PLA UCA (1 mg, negative control), and free TRAIL (10 ng, positive control representing the maximum TRAIL concentration used in the ligation step).

The results from a live/dead assay for the MDA-MB-231 breast cancer cells are shown in Figure 6. As expected, there is little cell death in both negative controls (6a – no treatment, 2.299 ± 0.347% cell death, and 6b – intact blank UCA, 0.519 ± 0.216% cell death), while a good deal of cell death (32.820 ± 0.796%) is evident in the free TRAIL positive control (6c). The cell death is characterized by both the red stained cells and the large black patches, which corresponds to areas where dead cells detached from the plate, with subsequent loss due to washing. For the ligated TRAIL groups, the live/dead assay indicates cell death for both intact UCA (8.296 ± 0.169%, 6d) and n-Sh (38.420 ± 0.020%, 6e). It can be observed in Figure 6 that the ligated TRAIL n-Sh were much more effective in inducing cell death in these susceptible cells. In fact, TRAIL-ligated n-Sh induced significantly more cell death than the intact TRAIL-UCA ($p < 0.0001$). Additionally, cell death induced by TRAIL-ligated n-Sh is significantly greater than treatment with free TRAIL ($p = 0.0098$). However, this result could be skewed based on the large patches of lost dead cells. In agreement with our expectations, we

saw little cell death in both control non-linker groups (6f – intact non-linker UCA, 2.397 ± 0.299%, and 6g – non-linker n-Sh, 2.020 ± 1.358%), which is not significantly different from the no treatment group ($p = 0.8502$ and $p = 0.8608$, respectively). The non-linker control group results indicate that the observed cell death effects are not incidental events due to release of physically adhered TRAIL, and that the active TRAIL molecules are those that are ligated to the UCA surface.

On the other hand, very little cell death is seen in the TRAIL-insensitive 3T3 fibroblasts, as expected as seen in Figure 7. The 3T3 cells were grown to 30% confluence, and after treatment very few, if any, red-stained dead cells are visible in any of the test groups. For comparison, the free TRAIL group (C) also shows very few dead cells, indicating that TRAIL has no effect on non-sensitive healthy cells. All 3T3 fibroblast samples exhibited less than 3% cell death (actual percentages given in Figure 7) in images collected. In all of these samples, the dark patches represent areas that were never populated with cells, and did not change throughout the experiment.

Discussion

In this proof of concept study, we have shown that ligation using maleimide chemistry is an effective method for attaching TRAIL to UCA, confirming our preliminary study.[40,41] We have now shown that these modified UCA maintained acoustic properties and induced cell death in susceptible cells, but not in resistant cells. Importantly, we also show that breast cancer cells treated with n-Sh generated by US treatment of ligated TRAIL-UCA exhibit the greatest extent of cell death among the test groups. This observation is consistent with the hypothesis that shattering a single UCA into n-Sh will produce an abundance of particles that can carry TRAIL to a greater population of susceptible cells than would be available for interaction with a single intact UCA. The added advantages of US interaction with micron-sized particles include radiation force pushing the UCA toward the leaky vasculature wall, UCA rupture due to US-induced inertial cavitation, and cavitation-induced generation of localized mechanical shock waves, microjets, free radicals, localized extreme temperatures (up to 5000 K), transient breaks in the already leaky vasculature.[42] and US-induced increases in tumor vasculature permeability.[43] Combined with these advantages, our results are encouraging for the future of *in situ* generation of nanoparticles. We describe a system utilizing dual-mechanism targeting: first, n-Sh are only generated where the US is focused on the tumor, and second, the surface-bound TRAIL is targeted to cell surface death receptors on cancer cells.

The double emulsion process for UCA manufacture that is described here is also quite versatile for encapsulation of drugs, bioactive molecules, or other species. US-guided delivery of hydrophobic species can be promoted by incorporating the drug into the organic phase, and the same can be said for hydrophilic species if incorporated into the aqueous phase.[5,34,36,44] One such example that we have studied is encapsulation of doxorubicin (Dox) within the PLA shell, which has been visualized using confocal microscopy.[33,34] Drugs such as Dox, 5-fluorouracil, paclitaxel, bortezomib, and actinomycin D have been shown to act synergistically with TRAIL and also to render resistant cancer cells susceptible to TRAIL.[25,30,45,46] Co-encapsulation of a bioactive molecule, such as bortezomib or doxorubicin, could greatly expand the scope in which these agents can provide effective therapy. Additionally, optimization of the US parameters for n-Sh generation from the functionalized UCA is ongoing. Future studies will further investigate the possibilities for TRAIL-functionalized UCA.

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Caesar's Palace, Las Vegas, Nevada, US

As the pharmaceutical landscape evolves, industry professionals are being asked to overcome an increasing number of challenges and accomplish more today.. Solutions are being sought to anticipated issues without the luxury of trial and error. Problem solving in the pharmaceutical industry is a small window with large consequences. ISPE recognizes all the current and future challenges to industry peers and in response has created a comprehensive event to address trends in the current pharmaceutical manufacturing market. The 2014 Annual Meeting in Las Vegas, Nevada will offer the latest industry information and manufacturing resources running parallel to a large gathering of professionals for networking and collaboration.

The immense and luxurious Caesar's Palace will host ISPE's Annual Meeting providing expertly designed presentation facilities to accommodate 200 speakers and professional participants, 13 educational tracks, more than 50 sessions, and a new exhibit layout featuring 175 exhibitors. Training will be held in multiple state-of-the-art rooms with the latest in communication abilities. The conference schedule provides ample time for visiting exhibits and networking with colleagues. ISPE's 2014 Annual Meeting is a chance for industry colleagues to tap into the pulse of pharmaceutical manufacturing in a city able to handle the heat. This premier event promises to address solutions to industry challenges as well as celebrate pharmaceutical manufacturing and the successes industry peers have worked so hard to accomplish.

ISPE is proud to present the following at its 2014 Annual Meeting:

Keynote Speaker

Dinesh Thakur, Executive Chairman at Medassure Global Compliance Corporation

Securing the Supply Chain: *Combating the Evolving Risks in Pharmaceutical Sourcing and Manufacturing*

Unprecedented regulatory actions such as the invocation of the Application Integrity Policy, a highly restrictive and cumbersome Consent Decree, and successive import alerts have emphasized the risks to the pharmaceutical supply chain, especially when sourcing API, intermediates, excipients from countries like India and China. Although the industry is beginning proactive measures in developed economies avoiding the supply of substandard and adulterated drugs, many pharmaceutical companies have not addressed these risks adequately. Using the prosecution of Ranbaxy Laboratories in the US as an example, Thakur (formerly Ranbaxy's Director and Global Head, Research Information and Portfolio Management, who reported the company's failings to the US FDA) focuses on the need for an independent, third-party monitoring of the supply chain to ensure consistency in the quality of medicines supplied to all countries.

Executive Series

Changes in the pharmaceutical industry can be demanding. Cost pressures, tighter schedules, the need for manufacturing flexibility, and shifting regulatory expectations are constant challenges affecting how stakeholders conduct daily business. Executives must manage such events with routine project leadership and optimizing techniques to assure positive impacts on planning, design, and capital undertakings. Inherent challenges lead to innovation in industry. Pharmaceutical executives must outline an organized path using efficient resources, time, and financial assets to accomplish manufacturing goals.

Annual Meeting Connection

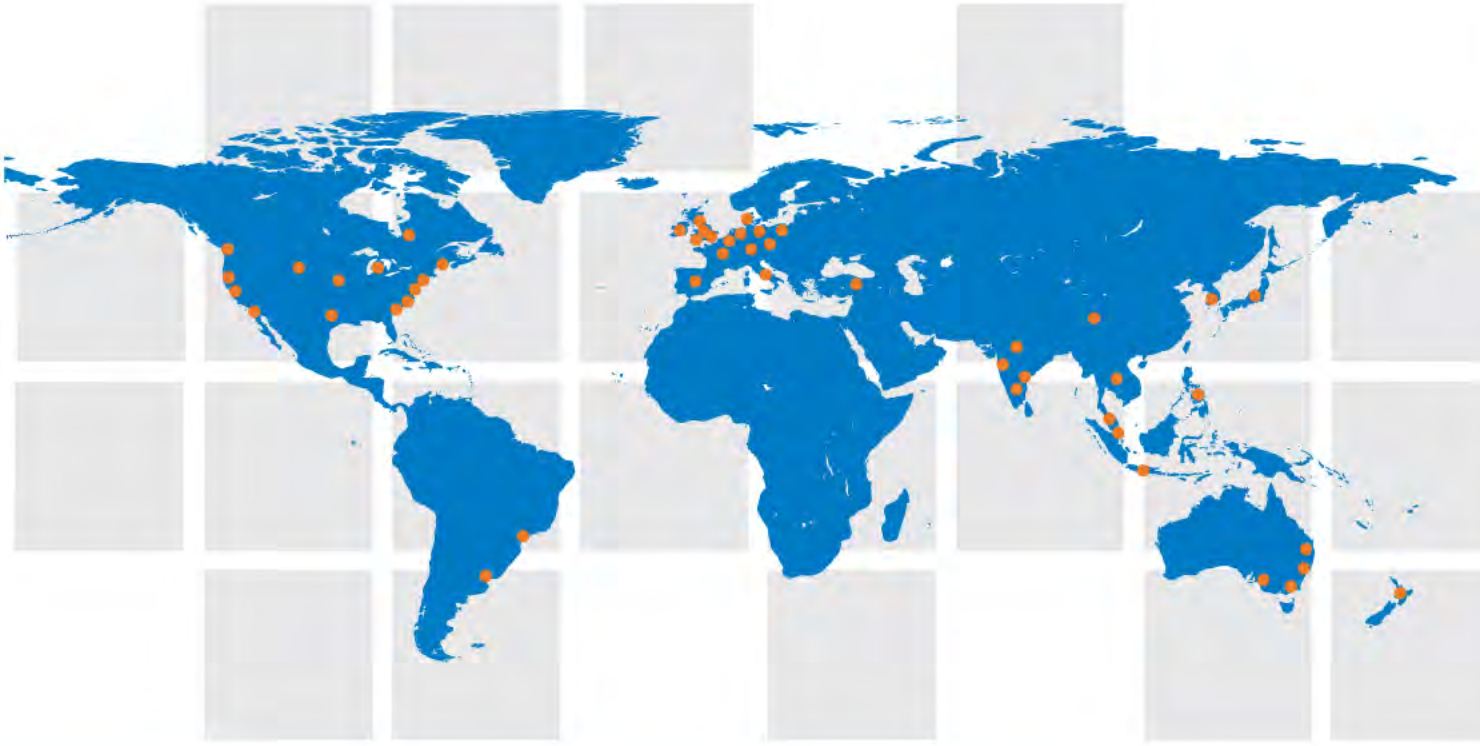
Presented by Executives for Executives

ISPE recognizes planning well for the future of an organization requires insight well beyond the day-to-day challenges. Executives can find value from their peers' experiences and beyond theory innovations to assist with their administrative vision. Using next generation designs, novel approaches in operational excellence, and modern and profitable product lines, executive collaboration can drive the pharmaceutical industry to an energetic edge of quality and profit.

Facility of the Year Awards (FOYA)

Learn about the innovative projects from the 2014 Facility of the Year Awards Category Winners. Be among the first to discover which project will be named the 2014 Facility of the Year Awards Overall Winner. The FOYA Program recognizes state-of-the-art pharmaceutical manufacturing projects which implement innovative technologies to improve product quality, reduce cost, and demonstrate advances in project delivery.

ISPE Affiliates and Chapters: Local Connections. Global Impact.



Boost your knowledge. Expand your network.

ISPE's Affiliates and Chapters are your local resource for all things ISPE—from translations of ISPE's world-renowned Guidance Documents to education on regional industry and regulatory trends.

Get involved with your regional Affiliate or Chapter to meet industry leaders in your area, contribute your expertise to industry-advancing initiatives at the local level and share best practices with like-minded professionals.

ISPE

Connecting a World of Pharmaceutical Knowledge

Get Involved With Your Affiliate or Chapter Today!
ISPE.org/Affiliates-and-Chapters

Objective:
Participants will benefit from applicable experience and innovative strategies developed by industry executives.

Session Topics:
- Facility of the Year Category Winners
- Facilities of the Future
- Operational Excellence
- Biotechnology FIT Talk Series
- Plasma Protein Manufacturing Facility

Notable Takeaways:
- Successful Biotech manufacturing strategies in operational excellence presented by FOYA Category Winners, Baxter Healthcare
- Tools needed address challenges and evolve facility processes to remain cutting-edge and relevant while delivering high quality medications

ISPE Guidance Document Connections
- *ISPE Guide: Biopharmaceutical Process Development and Manufacturing*

Program Committee Members

Advisor: Robert Chew, President, Commissioning Agents, Inc.
Chair: Gordon Leichter, Ph.D., Regional Sales Manager, Belimed, Inc.

Track Directors

Investigational Products: Steve Yoder, General Manager, Fisher Clinical Services
Information Systems: Randy Perez, Ph.D., Director, Information Governance Management, Novartis Pharmaceuticals
Manufacturing Facilities and Design: Jim Gazvoda, Principal, Flad Architects
Manufacturing Technology: Michelle Gonzalez, Principal, Biopharm Engineering Consultant
Project Management: Keith Gibbs, Director of Project Delivery, Innovative Process Solutions
Quality: Rose Mary Dollard, Director, Regulatory Compliance, Johnson & Johnson
Global Regulatory and Compliance: Steve Tyler, Director, Quality Assurance, AbbVie
Technical Showcases: Paul Egee, Vice President of Sales, IMA North America
Young Professionals: Jennifer Lauria-Clark, SE, Manager Technical Services, Commissioning Agents, Inc. and Brody Stara, Process Engineer, CRB Consulting Engineers

Information Systems

The integrity of laboratory data is crucial for audits and regulatory inspections. Compromised data impacts a manufacturer's bottom line and threatens the availability of therapeutic medicines. The industry is facing great pressure to produce pharmaceuticals at low cost while adhering to the highest safety and data integrity expectations. To meet the challenging demands of quality-driven, internal inspectors and safety-driven, government regulators, manufacturers are turning to innovative IT infrastructures. During clinical trials and regulatory reviews, an effective data management system can streamline budgetary requirements, as well as shorten development to market timelines. Complexity in global supply can be uniform through a structured, technology based network which establishes real-time data collection, storage, and sharing.

Today, advanced technology is exceedingly capable of contributing to a more secure global pharmaceutical manufacturing market. An important element of preserving the integrity of a product's lifecycle is the ability to track and trace through serialization and documentation of a product's inherent origins. In keeping with the core elements of GxP applications of traceability and accountability, drug manufacturers are implementing technological infrastructures capable of authenticating ingredients and products at any point on the global supply chain.

Complexity and necessary mid-process modifications are driving technological information systems toward a more agile software development trend in regards to computer validation. Agile software development incorporates a more flexible, general product development approach where teams work in cycles toward a common goal.

Annual Meeting Connection

Data Integrity and Beyond

The Information Systems track includes information, discussions, and workshops on a variety of topics important to the management, documentation, and compliance of the business of healthcare companies. Multiple sessions on the extremely hot topics of data integrity and serialization will be held. In addition, delegates will have an opportunity to learn about some of the work being done by ISPE related to the adoption and management of leading edge technologies like the use of mobile and cloud computing. Also of interest are a range of IT and automation related topics as varied as maintaining control of your computerized systems, the paperless laboratory, Agile software development of GxP applications, GxP IT infrastructure, and decommissioning a regulated system. Delegates who attend sessions within this track are sure to improve their understanding of the controls and requirements associated with implementing, managing, and retiring applications and data within the regulated environment.

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Interview with Gordon Leichter, Chair of ISPE Annual Meeting Planning Committee

Gordon Leichter, PhD, is currently the East Coast Sales Manager for Belimed Infection Control focusing on providing sterile processing equipment to the pharmaceutical manufacturing industry. He has more than 30 years of experience within the pharmaceutical industry manufacturing and marketing processing equipment. Leichter has been an active member of ISPE throughout his career, serving on a number of chapter boards, giving technical presentations, leading seminars, writing articles, participating and chairing various committees, as well as a leadership role on the 2006 Facility of the Year winning team. Currently, he is a Director on the ISPE International Board of Directors, as well as the President of the NJ ISPE Chapter. He has held positions as Chair of the Sterile Products Processing Community of Practice (SPP COP) and Chair of the ISPE Body of Knowledge Committee. He holds a BS in operations management and a MS in management from Thomas Edison State College and a Ph.D.in business administration from TUI University.

Why did you decide to chair the ISPE Annual Meeting Planning Committee this year?

I am an active ISPE volunteer and I enjoy being involved with different committees. Since I was the co-chair of the committee last year, it was a natural progression. The Annual Meeting is the Society's premiere event so it is a great experience to work with other motivated industry volunteers and the talented staff to deliver a top notch professional program.

What are your goals for the conference this year?

Our industry is quite dynamic and we are constantly facing change and challenges. I think this is evident within the Society as well. Working as a team, our goal is always to improve upon the event every year. The content this year is more robust than ever with more than 90 sessions in 10 different topic areas and the location is equally exciting. So, our goal is to attract as many members as possible to join us for this great educational and networking event. One of the things that is never lost on me as a volunteer leader, but also as an attendee, is what can learn from each other at this event. The face to face interaction and learning are what gives attendees a competitive edge in the face of the aforementioned climate. It truly cannot be replaced.

What is unique about this year's Annual Meeting?

We have increased the breadth and depth of the Executive Series to include more domestic and international regulatory topics. Additionally, one of our keynote speakers, Dinesh Thakur, Executive Chairman at Medassure Global Compliance Corporation, but perhaps better known as the whistleblower at Ranbaxy who exposed its pervasive pattern of fraud, will offer compelling insights into the impact of cases like Ranbaxy, and the impact of supplies from emerging markets and the correlation to drug shortages and patient safety. With so many companies sourcing supply from emerging economies, this presentation is quite timely and will resonate with all of us in the industry. Of course, we have to change the old adage to "what happens in Vegas will stay in Vegas." We are certain that with such robust, cutting-edge content, all of the attendees will take what they learn in Vegas and apply it! And of course the relationships developed will become beneficial in business dealings for years to come. Finally, we will have the unique opportunity to collectively thank and fondly bid farewell to Nancy Berg, our current CEO, and welcome officially the new CEO of ISPE.

What should people expect this year and why is that different from previous years?

Well, it sure will be warmer. The 5K runners will appreciate that, especially since the run this year will take place on the Vegas Strip and the winner will receive a free helicopter ride over the city. We brought back the Golf Tournament, which everyone is excited about! After collecting data for years on what drives attendees to register, we realized how important networking really is and so we have really made an effort to offer these opportunities throughout the program in a thoughtful and beneficial way. We are really proud of that. However, just like ISPE is known to do, we are offering the best content in the industry. Staff and volunteers have done an outstanding job to provide a flexible schedule that allows versatility with minimal overlap, which was in response to feedback received from the event last year. What is great about the ISPE staff is that they listen, digest and then adjust. Every year, the organization and execution of the event becomes smoother. It's a joy to work with such professionals. As for the overall program, we have some great recurring sessions such as Keith Gibbs' popular Project Management series and some more interactive ses-

Concludes on page 86.

Session Topics:

- Data Integrity
- Serialization
- Track & Trace
- Cyber Security
- IT Infrastructures
- GAMP V-Model in Agile Development

ISPE Guidance Document Connections

- *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems*
- *GAMP® Good Practice Guides:*
  - *A Risk-Based Approach to Electronic Records and Signatures*
  - *A Risk-Based Approach to GxP Compliant Laboratory Computerized Systems (Second Edition)*
  - *A Risk-Based Approach to Testing of GxP Systems (Second Edition)*
  - *Electronic Data Archiving*
  - *A Risk-Based Approach to Operation of GxP Computerized Systems – A Companion Volume to GAMP® 5*
  - *IT Infrastructure Control and Compliance*

Investigational Products

In today's economy, expenses in bringing a new pharmaceutical compound to the commercialized market could reach more than $ 1 billion. All pharmaceutical stakeholders face the same rudiments in development: time and risk. Industry developers dealing with investigational products (clinical trial materials) are searching for areas to streamline supply chain sourcing, establish robust clinical trial data management systems, expedite approvals of new drug therapies, and keep company investments safe and predictable.

The undiminished trend in globalizing clinical trials, alliances, and collaborations is driving industry innovation and progress. Pharmaceutical trials are quickly expanding to involve intricate emerging markets with a diversity in stakeholders unparalleled to the past.As the geographic spread intensifies, manufacturers face unprecedented strategy choices and varied opportunities for sourcing. Ambient and cold chain distribution along the supply chain carry new risks as trajectories expand along with present exigency. The new generation of clinical trial supplies includes advantageous breakthroughs to improve the supply chain and drive clinical supply management into an idealistic future.

Cloud-based computing and advances in electronic

Interview with Gordon Leichter

Continued from page 85.

sions with suppliers. We developed our tracks based on response from past attendees and so there is something for everyone. Especially, since the economic downturn in 2008 when so many of us are being asked to do three jobs in addition to those we were already doing, we are having to keep up with areas that were once not part of our responsibility The ISPE Annual Meeting is set-up to allow delegates who have business obligations in different areas attend education that they will benefit from. You really get your money's worth.

Any favorite sessions you are looking forward to?

That's a tough question because there are so many good choices. However, as previously mentioned, the schedule will allow for more flexibility to attend more of the varied sessions. My personal favorites are the case studies where you can learn from world class execution models, as well as challenges that others have experienced. I am looking forward to Dinesh Thakur's talk about his involvement in the Ranbaxy situation – that will be quite interesting! Of course, what ISPE is doing in Drug Shortage, Metrics and Patients Safety are always popular and most of the time standing room only. I look forward to those, if I can find a seat. I am also excited about the technology sessions where suppliers are able to showcase their product solutions in a non-commercial atmosphere. It is so important that suppliers and delegates have these conversations because many times this is where problems are solved and business is advanced. It sounds cliché to say, but you really do loose a competitive advantage by not attending.

Anything you learned or were surprised by in your work planning the 2014 Annual Meeting?

Well the first thing I learned from this experience is that the staff sure works darn hard to pull this event off. Also, the volunteer course leaders and all the speakers really put in quite an impressive and enthusiastic effort. I think the allure of Vegas is Going to be a draw. The last time we were in Vegas it was one of the largest meetings in ISPE's history. Face it, we are all devoted professionals and work really hard, and the underlying reason for the Annual Meeting is so ALL members globally have an opportunity to interact and expand our knowledge and experience, so why not do it in Vegas. See you there!

labeling lay the foundations for practical approaches to an increasing number of global opportunities. Manufacturers using the latest technology can gain deeper knowledge of sourcing and unfamiliar regional risk factors. Efficient data networks with documentation sourcing from multiple suppliers can be the key to uninterrupted clinical studies and practical data mapping for regulatory documentation. The ability to establish real time data networks and adapt to variables in emerging markets can also enable companies to securely elevate their investigational and developmental products into the future of pharmaceutical clinical supplies.

Annual Meeting Connection

Playing the Winning Hand

The Investigational Products (Clinical Trial Materials) track, Playing the Winning Hand, will include presentations and real world insights from industry leaders sharing their knowledge and experience as it relates to clinical sites and patient usage. Day one will embrace a visionary view of the future of clinical supplies, provide real-world insights into the current environment of the clinical site in order to enhance and expand clinicians and patients perspectives of clinical trials. Days two through three will correlate case studies and practicums relating to biotechnology and other pharmaceutical companies implementing new technology to manage and simplify the supply chain. Playing the Winning Hand will connect pharmaceutical investigational products with significant advances in e-labeling, technologies ambient and cold chain distribution management, and current guidelines in expanded access programs.

Objective:

Participants will benefit from topics critical to managing clinical supplies.

Session Topics:

- The Future of Clinical Supplies
- Next Generation of Investigational Products
- Technology and Innovation to Manage and Improve the Supply Chain
- Investigational Hot Topics
- Breakthroughs in E-Labeling
- Managing Ambient and Cold Chain Distribution
- Expanded Access Programs

Notable Takeaways:

- Proven applications of innovative technology in biotechnology and pharmaceutical manufacturing
- Applicable breakthroughs and management implementation through e-labeling
- Latest regulatory updates in expanded access programs

ISPE Guidance Document Connections

- *ISPE Good Practice Guides:*
  - *Booklet Labels*
  - *Clinical Supply Systems*
  - *Cold Chain Management*
  - *Development of Investigational Therapeutic Biological Products*
  - *Comparator Management*
- *Comprehensive Guide to Clinical Materials – A Handbook for Training Clinical Materials Professionals*

Manufacturing Facilities and Design

Innovation and sustainability are at the forefront of the pharmaceutical industry's desire for lean quality and design success. Long-standing systematic models are fading as manufacturers demand a new level of propagation to match recent changes in manufacturing strategies and solutions. Modern tactics such as reliability design incorporate proactive stances at the initial design stage providing cost-effective maintainability and functionality to continuous improvement. Essential elements of contemporary quality systems are also being addressed through modular opportunities. Flexible construction and cost-effective manufacturing strategies can give established manufacturers and emerging markets opportunities to rise to the competitive advantage. By harnessing technologies and methods, companies can remain viable in today's aggressively regulated and highly collaborative market.

Annual Meeting Connection

Innovative Approaches and New Tools for Design Success

Sustainability/Lean Quality Results

Objective:

Comprehend essential aspects of modern approaches for facility design, sustainability, and cost-effective manufacturing.

ISPE offers two comprehensive streams of content related to manufacturing facilities for delegates committed to innovation and sustainability.

Session Topics:

Innovative Approaches and New Tools for Design Success

- Reliability- Centered Design/Life Cycle Cost (LCC)
- Advanced Development & Manufacturing (ADM)
- Supply Chain Strategy
- Single-Use Solutions
- Cost-Effective Manufacturing Strategies & Solutions
- Modeling Tools for Master Planning and Product Improvements
- Modular Opportunities and Viewpoints

Sustainability/Lean Quality Results

- Optimization Modeling Tools
- CAPEX/OPEX Investments
- Steam System Optimization
- CIP/SIP Operational Sustainability
- Chilled Water Energy Efficiency
- Carbon Modeling Decision Making
- Lean Organization, Problem Solving & Systems Application

Notable Takeaways:

- Essential elements to Advanced Development and Manufacturing (ADM)
- Applications and comparisons between Capital Expenditure (CAPEX) and Operational Expenditure (OPEX)
- Continued quality guidance for cleaning-in-place and sterilization-in-place

ISPE Guidance Document Connections

- *ISPE Baseline® Guide: Biopharmaceutical Manufacturing Facilities (Second Edition)*

Manufacturing Technology

Pharmaceutical manufacturing is expanding its traditional view on data. The future state of advanced manufacturing processes is in real-time operational data. Manufacturing technology prospects are being established in highly networked and analytical systems that generate applicable data used in proactive decision making. With a dynamic and dependable flow of data all aspects of manufacturing can work in harmony resulting in a low risk, highly productive business operation. Regulation can be positively impacted as manufacturing managers and IT operations collaborate to identify systems that support the common goals of sustainability, predictability, and efficiency.

Annual Meeting Connection

The Manufacturing Technology track is a unique opportunity for professionals to participate in a comprehensive trajectory incorporating the latest advances in aseptic processing, containment, blow-fill-seal, and single-use technologies.

Objective:

Participants will benefit from interactive and solution-focused sessions addressing Quality by Design (QbD) and operational excellence.

Session Topics:

- Containment of Potent Compounds
- Advanced Aseptic Processing
- Modelling within the QbD framework
- Blow-Fill-Seal Technology
- Scale-Up of Single-Use Technology
- Critical Utilities Overview
- The Impact of Manufacturing Reliability
- Integrated Manufacturing Control Strategy
- Cleaning Program for a Multiproduct Biopharmaceutical Facility
- Risk Based Approach to Reduce Cleaning Validation for IMP Products
- Quantitative Image Processing for Cleaning Validation and Verification
- Improving Product Yield in Sterile Drug Product Manufacturing
- Particle Reduction during Component / Closure Processing
- Aseptic Blow/Fill/Seal packaging Technology with Heat Sensitive Products
- Benchmarking Study of Container Closure Integrity

Notable Takeaways:

- ISPE Critical Utilities Community of Practice (CU-COP) overview session introducing the latest changes to the ISPE – "Water and Steam C&Q Guide"
- Joint discussion of an in-depth synopsis of the upcoming ISPE "Sampling Guide"

Project Management

Managing people is a key component of project management. Project managers have the responsibility to use robust moderation tools and properly engage stakeholders to identify and mitigate risk. Early engagement with a project execution plan can establish system solutions for beneficial lifestyle management requirements. Success in project management goes beyond completion. Adhering to restricted timelines and budgets presents challenges for any manager in charge of accomplishing major tasks in such a highly regulated environment. Often times, managers must deal with the reality going against even the most carefully planned project. If key elements of a quality system are established early, overcoming hurdles and unexpected issues will resolve with the lowest impact and the highest odds for success.

Annual Meeting Connection

Don't Gamble Your Project Away: Real World Lessons of Project Management

Educational speakers will provide interactive workshops focusing on the values ISPE's Project Management Good Practice Guide brings to projects, specifically those executed in the biopharmaceutical sector and other highly regulated industries.

Objective:

Participants will gain technical knowledge to apply risk assessment tools and project planning methodologies.

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Interview with Dinesh Thakur, ISPE Annual Meeting Keynote Speaker and Executive Chairman at Medassure Global Compliance Corporation

Dinesh S. Thakur is an expert and accomplished entrepreneur in pharmaceuticals, biomedical product development, drug regulation, and information technology. During his career, he held senior positions at Bristol-Myers Squibb Company, Ranbaxy Laboratories, and Infosys Technologies. Most recently, he co-founded and was the Chief Executive Officer of Sciformix Corporation, a scientific processing outsourcing organization that delivers services in the areas of drug safety, biometrics, medical and regulatory writing, and clinical operations. From 2003 to 2005, Thakur was the Director and Global Head, Research Information and Portfolio Management at Ranbaxy Laboratories, India's largest generic drug manufacturer. He was responsible for managing research and development information for generic drug development, manufacturing, and commercial operations. In addition, he implemented automated systems to capture research and development data for global regulatory submissions, compliance, and manufacturing. While at Ranbaxy, Thakur discovered that the company was falsifying drug data and violating current good manufacturing practices and good laboratory practices. He resigned in 2005 after reporting the fraud to company management, and worked with authorities for eight years to unravel the complicated trail of falsified records and dangerous manufacturing practices. In May 2013, Ranbaxy pleaded guilty to multiple criminal felonies and agreed to pay $500 million to resolve criminal and civil allegations of falsified drug data and systemic manufacturing violations resulting in substandard and unapproved drugs. The groundbreaking settlement is the largest of its kind against a generic drug manufacturer. Thakur received a Bachelor's degree in technology from Osmania University, an MS in chemical engineering from University of New Hampshire, and graduate training from Syracuse University.

Since Ranbaxy, how have regulators and regulations evolved to recognize manufacturers attempting to manipulate the system? What are pharmaceutical companies experiencing now that is a direct result of Ranbaxy's falsifications?

Clearly, there is more awareness at the US FDA and the UK MHRA that data integrity problems are a lot more pervasive than originally thought. There is widespread acceptance that economically motivated adulteration is real and poses a significant threat to the quality of our drug supply. Therefore, inspectors are now conducting "forensic" audits explicitly looking for evidence of fraud, like discarded raw data, evidence of testing into compliance, false evidence of stability testing, etc. The regulations themselves remain largely unchanged, just that regulators are now allocating additional resources to monitor such activities. The US FDA has provided a focus to this effort through the newly established Office of Pharmaceutical Quality. The regulatory actions at Ranbaxy and Wockhardt have had material impact. In addition to loss of reputation, these actions have had a significant financial impact. As far as global pharmaceutical companies are concerned, I haven't seen a major change in their approach to managing their upstream supply chain from foreign locations in public. I think companies recognize the inherent risks, but have yet to undertake a systematic ongoing evaluation of their sourcing processes to identify risks and adopt appropriate mitigation strategies yet.

Ranbaxy was the sole manufacturer of many of the generics it produced. What steps should government agencies take to assure if the need arises, ceasing medicinal imports from one company doesn't ignite shortages of critical medications?

Over the past few years, we have seen that more than 60% of all drug shortages in the US arise from generic drugs. According to a recent US Government Accountability Office Study, supply disruptions stemming from quality problems are a major cause of drug shortages. One of the factors that drive such situations is the inability of the market to reward quality. Generic drugs primarily compete on price, often at the expense of quality, and this is a major contributing factor.

There is a concerted effort underway at the US FDA to try and quantify the risk to the supply of single source generic medicines, especially from foreign manufacturers. The Agency is focusing on advance notification and communication, which would help us plan better. Upgrading ageing manufacturing facilities, automation of the manufacturing processes, reducing market concentration through economic incentives, and building

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Interview with Dinesh Thakur

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redundancies in the supply chain will all help alleviate this situation in the long run. There also is a lot of focus on the way we measure quality; statistical quality control techniques haven't been incorporated into the pharma manufacturing process to the same extent as they are in other industries. The important thing is that the Agency has recognized this problem and is working toward a solution. FDASIA 705 is enabling the use of leading indicators rather than relying on approaches that used criteria like the recall rate as evidence of systems failure. Data collected under FDASIA 706 ahead of an inspection makes it possible now to measure both performance (and therefore trends) in addition to compliance. This is a good start.

What advances in technology are becoming more critical to regulators searching for valid data and real-time research analysis?

There are three specific areas in which technology can enable this process:

1. Access – technology can enable us to conduct remote audits, as envisioned in FDASIA. This addresses one of the key challenges in providing closer scrutiny, namely our inability to conduct frequent audits and inspections of overseas facilities.
2. Frequency – an inspection is often a point-in-time snap shot, but access to systems at manufacturers' can provide regulators with near real time access to data. Analysis of such data (e.g., batch production records) will enable us to monitor deviations from the standard process more effectively.
3. Data Analytics – the ability to study large data sets in order to identify trends and patterns is another potential area where technology can help. This problem has been solved in other areas like fraud detection in credit card transactions. Models such as these can be applied to the pharmaceutical supply chain to get advance notice of "questionable" transactions which then enable us to focus on them more diligently.

Ranbaxy was a unique situation crossing international boundaries and involving many links in the supply chain, what lessons do you think are most important to share from your experiences working with the FDA and the Department of Justice? What can manufacturers continue to take away from Ranbaxy's aftermath?

Working across international boundaries is becoming commonplace, the pharmaceutical supply chain is becoming increasingly complex due to the fragmented and global sourcing of APIs, intermediates and excipients coupled with manufacturing processes that now contain multiple handoffs. API and excipient vendors (whom the pharmaceutical companies rely on) are themselves outsourcing production of raw materials thus creating a chain of handoffs. Global regulators too have increased their focus on these issues. We have seen this in many cases like heparin, ethylene glycol, melamine contamination, etc. There are multiple intermediaries and hand-offs and trying to trace the source of a specific API is often not feasible as most of these providers are foreign.

The lesson for large pharma, or for that matter, any company that sources from facilities located overseas is that you really need "feet on the ground" to monitor the process continuously for "risks" that may enter your supply chain. Conducting an audit once a year and relying on Certificates of Analyses from the overseas manufacturers is not adequate.

I hope the regulators have learned that there are significant cultural differences that become real challenges when conducting an inspection. Trying to translate their experience from US facilities to those located overseas doesn't always work. It is important to have the right context when working overseas, where the business environment is markedly different from the US or the UK, where facilities are often located in remote places that can only be accessible with the help of people who work at that manufacturer; language becomes a barrier to communication, hierarchical organizational structures often dictate what you want to hear, etc.

Last but not the least, the DOJ has publicly said that they intend to apply the Park Doctrine and hold executives in the industry responsible for the kind of behavior that we have seen at Ranbaxy. This is clearly a departure from the past where the corporate entity pled guilty; going forward individual executives are going to be held accountable. I think this is a major shift in law enforcement and the industry needs to pay attention to this new paradigm.

What positive developments in the pharmaceutical industry since Ranbaxy, both in manufacturing and regulating, can you cite as constructive progress toward safer and more efficient medicines for our global population?

The most significant development in recent years is the approval of the FDASIA regulation by the US Congress. The FDA now has resources to better regulate foreign manufactur-

Interview with Dinesh Thakur

Continued.

ers, study the quality of the drugs on the US market and collaborate with other national regulators and share data/findings among the regulatory agencies. While these are positive and constructive steps toward ensuring safe and effective medicines, much still remains to be done, like proactive monitoring of the upstream supply chain to ensure high confidence in the quality of our drugs.

The regulators in Europe, EMEA and MHRA also have taken similar actions against overseas companies that commit fraud. MHRA has been very vocal about their concerns with data integrity at foreign manufacturing locations. There is clearly a major initiative among global regulators to share and learn from each other's experience in evaluating and enforcing compliance at overseas manufacturing locations.

In the US, the FDA has announced testing of commercially available products manufactured overseas which it had never done before. Clearly, this is a step in the right direction.

What steps have other generic manufacturers who produce quality products taken to rebuild confidence in the non-brand medicines they produce?

Generic drug manufacturers have committed to upgrading their manufacturing facilities, introducing automation and retraining their workforce in cGMP. However, cultural barriers remain and this is a long term problem that manufacturers who produce good quality generic drugs will have to continue to address.

Another key area is to adopt a single global quality standard that meets the needs of all markets. Varying standards across countries has been at the root of some of the issues we have seen in the past.

A few generic manufacturers have begun to proactively monitor upstream processes for quality and data integrity. Recognizing that sourcing from India and China is here to stay, these companies have begun instituting active monitoring processes for every batch of API, excipient and intermediates that they import to formulate their drug product. Our experience working with them has been very positive so far.

What do you believe are the most important steps in the pharmaceutical checks and balances in regard to the global supply chain?

Pharmaceutical companies have evolved over the years to comply with regulations regarding strength and purity of their products. They have established reasonable controls over what occurs within their facilities. However, these actions do not address the need for increased visibility and controls over global vendors who supply the materials that make up the final product. The need is for continuous assessment of risk to effect mitigation and remediation in a timely manner. A few elements of the checks that we have found useful in our engagements are:

- Continuous assessment of partners/vendors using critical-to-quality parameters in a non-intrusive manner
- Focus on assessment through preventive (through remote monitoring) and corrective (audits and remediation) components
- Supply chain fraud-detection analytics as part of the monitoring and analysis

What elements do you find critical for quality processes when approaching safety and efficacy in pharmaceutical global supply?

The specific elements vary based on the nature of the supply chain and the manufacturing process. In general, a combination of quantitative measures (both leading and lagging) and qualitative measures is recommended. Medassure has developed a comprehensive list of indicators which we use when monitoring the supply chain on a continuous basis. Specific parameters are selected based on an assessment to facilitate continuous monitoring and collection of data.

Why did you accept the invitation from ISPE to present at our 2014 Annual Meeting?

Having gone through this experience and looking at this problem from multiple facets, including industry's point of view, regulator, and law enforcement, I have developed a unique perspective. I have used all of this experience and distilled it into a solution framework that MedAssure offers to the industry. I believe that this solution will detect and manage the risk from sourcing globally proactively in a manner that is more innovative and effective. My hope is that application of this framework will allow for a safer and more secure upstream drug supply chain.

Given that ISPE events like the Annual Meeting offers an opportunity for industry leaders to congregate and discuss common problems, I am hoping to draw attention to this problem and offer a solution that I think would be useful.

What will be the focus of your presentation?

The presentation focuses on evolving supply chain risks around sourcing and manufacturing facing the industry today. It also covers

Concludes on page 92.

Session Topics:

- Top Ten Lessons Learned: A Study in Project Management
- Calculating Odds of Success: A Workshop on Project Management
- Developing Project Lifecycle Management Requirements: A Study in Project Management
- Developing a Project Execution Plan: A Workshop on Project Management
- Developing a Risk Assessment Based Culture to streamline the Project Lifecycle: A Study in Project Management
- Risk Assessment Tools and their Application: A Workshop on Project Management
- Developing a Project Procurement Plan: A Study in Project Management
- Procurement on Trial: A Workshop on Project Management
- The T.R.U.E. Cost of Project Safety: A Study in Project Management
- Updates on the Development of Specifications for Project Management e-based tools and Project Management COP Meeting

Notable Takeaways:

- "Crash Course" on the project managers role in safety
- Development of specifications for e-based project management tools for project managers
- Highlighted application of project management with keynote presentations featuring the Baxter, Covington, GA, facility and the design/construction of the Las Vegas Convention Center

ISPE Guidance Document Connections

- *ISPE Good Practice Guide: Maintenance*
- *ISPE Good Practice Guide: Project Management for the Pharmaceutical Industry*

Quality

The pharmaceutical industry is responsible for persistently guaranteeing product quality. Understanding manufacturing systems and processes is a fundamental element to adhering to the role of quality assurance in medicines. Identifying key attributes and implementing appropriate strategies to control the qualities is an evolving challenge. To successfully manage quality, these efforts must be integrated throughout the lifecycle of the product from design through routine production. The FDA regularly indicates the use of risk based approaches intrinsically dependent on process understanding and establishing a culture of quality to drive today's operational excellence in the pharmaceutical manufacturing field.

Annual Meeting Connection

The quality sessions provide an overview of several key aspects of a Robust Quality Management System (QMS) including practical solutions for implementation.

Objective:

Participants will discover how to use a QMS as a business driver and apply flawless QMS integration within an organization's fundamental structure and system processes.

Session Topics:

- Solutions for QbD and ASTM E2500 Implementation
- Operations Focused Quality System Optimization
- How Good is Your Auditing System?
- Operational Excellence
- Key Elements of a Quality System
- Quality Culture and Continuous Improvement
- Translating Laboratory Developed Visible Residue Limits (VRL) to the Manufacturing Floor

Notable Takeaways:

- Management for QMS continuous improvement to drive operational excellence
- Interpretation of quality metrics to better define a sustainable culture of quality
- Optimization strategies through innovative approaches to operator engagement and training

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Interview with Dinesh Thakur

Continued from page 91.

methodologies that an organization can use to identify and mitigate these risks proactively.

Is there anything else you would like to say to ISPE members?

Globalization of the pharmaceutical supply chain has introduced new vulnerabilities in the manufacture and distribution of drugs. The fragmented and globalized pharmaceutical supply chain requires new and innovative methodologies to track and assess. It is important for the industry to better understand these risks and proactively mitigate them before they become too big to handle. The cost of remediation is very large, as we have seen from the consent decrees that have been issued over the last few years. Addressing upstream risks to the supply chain is an important area for pharmaceutical manufacturers to consider now.

ISPE Guidance Document Connections

- *Product Quality Lifecycle Implementation (PQLI) from Concept to Continual Improvement Guide Series*
  - *Part 1: Product Realization using QbD, Concepts and Principles*
  - *Part 2: Product Realization using QbD, Illustrative Example*
  - *Part 3: Change Management System as a Key Element of a Pharmaceutical Quality System*
  - *Part 4: Process Performance and Product Quality Monitoring System (PP&PQMS)*

Global Regulatory and Compliance

Pharmaceutical manufacturing is an increasingly global effort comprising a number of diverse variables. The potential of emerging markets drives prospects from established regulated markets to new frontiers of lower cost ingredients and higher product yields. However, manufacturers are still responsible for the safety and efficiency of their product and must develop and implement a global regulatory strategy to provide therapeutic medicines to the patients they service. Collaboration with local and global markets will assist in forming partnerships with regulation authorities ensuring all quality and safety systems span the complete spectrum of a product's development.

Annual Meeting Connection

Understanding and Mitigating Risk – The Eye of the Beholder

Presenters will analyze revealing case studies to clarify regulatory perspectives and explore industry leaders' insights to encourage preparedness and positive mitigating actions within a company operating culture. Speakers will present guidance in continuous manufacturing process design and implementation, global harmonization, Latin American regulatory climate, biotech QbD, ICH Q7, and raw materials.

Objective:

Participants will gain a new level of understanding through participation in practical and relevant discussions focused on proactive approaches to compliance in a global environment.

Session Topics:

- Risk
- Continuous Manufacturing
- Biotech/QbD
- Metrics
- Process Validation
- Global Harmonization
- Latin American Regulatory Challenges
- ICH Q7 and Raw Materials
- Drug Shortages

Schedule at a Glance

Visit the website for updated schedule.
www.ISPE.org/2014AM

Saturday, 11 October

08.00 – 17.00	Registration Open
18.00 – 19.30	Leadership Reception (Invitation Only)

Sunday, 12 October

07.30 – 16.00	Exhibit Hall Set-up
07.30 – 18.00	Registration Open
08.30 – 10.00	Student Poster Competition Set-Up
12.30 – 13.30	Young Professionals/Student Luncheon and Orientation
15.30 – 17.00	Opening Keynote Session
17.00 – 19.00	Welcome Reception in Exhibit Hall
17.00 – 19.00	Exhibit Hall Hours

Monday, 13 October

07.00 – 17.30	Registration Open
07.45 – 08.45	New Member and First-Time Attendee Orientation and Networking Breakfast
08.15 – 08.45	Young Professionals Meet and Greet
09.00 – 10.30	Keynote Session
10.30 – 12.30	Lunch and Networking in Exhibit Hall
10.30 – 16.00	Exhibit Hall Hours
12.30 – 14.30	Education Sessions
13.30 – 17.00	International Student Poster Competition
14.30 – 15.30	Exhibit Hall Break
15.30 – 17.30	Education Sessions
19.30 – 22.00	Young Professionals Event at Margaritaville
Evening	Open Night in Vegas!

Tuesday, 14 October

07.00 – 17.00	Registration Open
07.45 – 08.10	Young Professionals Meet and Greet
08.00 – 16.30	Technology Transfer Training Course
08.15 – 09.30	Education Sessions
09.30 – 10.15	Exhibit Hall Break
09.30 – 16.00	Exhibit Hall Hours
10.15 – 11.30	Education Sessions
11.30 – 13.00	Membership Luncheon
11.30 – 13.00	Exhibitor Lunch with Jefferson Davis
13.00 – 14.30	Education Sessions
14.30 – 15.30	Exhibit Hall Break
15.30 – 17.00	Education Sessions
19.00 – 22.00	Tuesday Night Party

Wednesday, 15 October

07.00 – 13.00	Registration Open
07.30 – 07.55	Young Professionals Meet and Greet
08.00 – 09.15	Education Sessions
08.00 – 16.30	Technology Transfer Training Course
09.15 – 10.30	Brunch and Networking in Exhibit Hall
11.00 – 13.00	Education Sessions
11.00 – 18.00	Golf Tournament
13.00 – 18.00	Hoover Dam Tour

Notable Takeaways:
- Recent developments in process validation
- Prevention strategies to mitigate drug shortages
- Current progress with ISPE's quality metrics initiative

ISPE Guidance Document Connections
- *GAMP® Good Practice Guide: Global Information Systems Control and Compliance*

Young Professionals

ISPE supports young professionals in the industry to foster ideas and professional needs of individuals who consider themselves new to their career in the biotechnology and pharmaceutical manufacturing industries. The Society, as an educational liaison, provides young professionals with cutting edge manufacturing knowledge, career/professional development, and industry networking.

Annual Meeting Connection

Good Quality Starts with the Basics

If you are a recent graduate or are new to the industry, this all-inclusive track is developed for young professionals or existing manufacturing professionals looking to enhance their education with the basics of good quality. The track contains dynamic sessions including round tables, case studies, and proactive discussions on the quality aspects of critical utilities, GAMP, facility design, and many more!

Objective:

Participants will enhance their foundational knowledge of quality, design, and operational excellence.

Session Topics:
- Silicone tubing extractables and their connection to particulates
- Project and operating challenges in GCP systems
- Designing for operational excellence
- A strategy to eliminate 483/regulatory observations
- Critical utilities 101 and 102

Notable Takeaways:
- Round table discussions focusing on solutions to operating challenges in GCP systems
- Design strategies for operational excellence

Young Professionals Meet and Greets

Sunday, 12 October 12.30 – 13.30
(Student Luncheon and Orientation)

Monday, 13 October 08.15 – 08.45

Tuesday, 14 October 07.45 – 08.10

Wednesday, 15 October 07.30 – 07.55

Young Professional Activities

Sunday, 12 October

12.30 – 13.30	Student Poster Competition Set-Up

Monday, 13 October

07.45 – 08.45	New Member and First Time Attendee Orientation and Networking
13.30 – 17.00	International Student Poster Competition
19.30 – 22.00	Young Professionals Event at Margaritaville

Technical Showcases

The Latest in Scientific Advances

Explore the latest implementations of technological products available to minimize cost and maximize both efficiency and safety. The Showcases offer an opportunity in a non-commercial environment to learn the science behind the advances so you are well informed when you are ready to visit with the Exhibitors.

Exhibit Hall Events

The exhibit hall at the 2014 ISPE Annual Meeting will be centrally located to the education sessions so delegates and

Concludes on page 96.

Annual Meeting Sponsors

2014 Pinnacle Sponsors – Azzur Group, Commissioning Agents, NNE Pharmaplan

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ISPE Hosts Training Workshop for Chinese GMP Regulators

by Qing Chen, Helena Baiao, Vee Revithi, and Bob Tribe

A training workshop related to quality system requirements for GMP inspectorates was organized in parallel with the ISPE China Conference held in Shanghai on 21to 22 April 2014. ISPE hosted the workshop in cooperation with the Centre for Food and Drug Inspection (FDI) of CFDA, the China Centre for Food and Drug International Exchange (CCFDIE) and a representative from the the Pharmaceutical Inspection Cooperation Scheme (PIC/S).

Approximately 100 Chinese regulators, who were the heads and quality managers of the provincial FDI's throughout China as well as officers from FDI of CFDA, participated in the workshop. The workshop trainers included:

Helena Baiao, Scientific Advisor Manager, INFARMED, Portugal; former Chair of PIC/S (2012 to 2013); current member of the PIC/S Executive Bureau

Bob Tribe, ISPE Regulatory Affairs Advisor for Asia Pacific; former Chair of PIC/S (2000-2001), former Chief GMP Inspector, TGA, Australia (1980 to 2003)

Dr Vee Revithi, Head of External Relations Europe, Roche, Switzerland; former Head of GMP, EOF, Greece; former member of the PIC/S Executive Bureau (2009 to 2013)

The trainers gave presentations on the following topics:

- Helena Baiao: PIC/S Update information, PIC/S recommendations on a QS of a GMP Inspectorate, Risk Approach in Inspection Scheduling, Attributes of a GMP Inspector

Workshop trainers and organizers. From left, Bob Tribe, Vee Revithi, Qing Chen, Zhu Ye, Helena Baiao (standing).

Workshop audience.

- Bob Tribe: PIC/S Inspection procedure, Common Challenges Prior to Being Assessed for PIC/S Membership
- Vee Revithi: PIC/S Accession Procedure, PIC/S Audit Check List

At the beginning of this year, the CFDA decided to streamline the GMP supervision of pharmaceutical manufacturers by changing the previous two-level GMP inspection model to a decentralized, one-level model, i.e., transferring all GMP inspections of the sterile product and the biological product manufacturers to the provincial FDIs (GMP inspections of non-sterile manufacturers had already been decentralized). This significant change required that a higher priority needed to be given to strengthen the management and technical capability of all provincial GMP inspectorates, starting with their respective quality system requirements. Furthermore, as the aim of CFDA is to harmonize its GMPs with international requirements and to eventually apply for PIC/S membership, the workshop was very useful and timely for helping CFDA to achieve these aims.

Very positive feedback was received during and after the event from all the regulators and agencies that participated in the program.

Shen Chuan Yong, the Vice Director of State FDI said that: *"All participants had learnt a lot from this workshop and it had been very useful for all the provincial FDIs to enhance their capability and improve their Quality Systems."*

Chen Yan, the Vice Director of Division II of State FDI said that: *"This was the first time for many of the participants*

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Training Workshop

Continued from page 95.

to learn about the PIC/S accession procedure in a way that was so clear and in so much detail."

They both thought that the workshop was a milestone for assisting all the provincial inspectorates in China to establish or improve their quality systems and therefore give more confidence for CFDA's application to join PIC/S.

It is expected that similar training workshops hosted by ISPE will be conducted in the future for the regulators of the Chinese Provincial FDIs to learn more about PIC/S procedures and approaches.

This kind of forum is an important step in facilitating networking and harmonization between PIC/S and the GMP regulators of China.

Shen Chuan Yong (5th from right) with Helena Baiao and Vee Revithi and some workshop participants.

ISPE Annual Meeting – Preview

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exhibitors have maximum opportunities to interact and share ideas. The open-plan ballroom for this year's exhibit hall will provide a vital networking hub in the heart of the Annual Meeting activity.

Visit identified Exhibit Hall Give-Away Sponsors' Table Top Exhibits and have your entry card stamped. Drop your completed card into the drawing tumbler for a chance to win one of several prizes. Must be present to win. Only registered Education or Training Delegates eligible.

Exhibit Hall Schedule

Sunday, 12 October 17.00 – 19.00

07.30 – 16.00 Exhibitor Set-Up
17.00 – 19.00 Welcome Reception

Monday, 13 October 10.30 – 16.00

10.30 – 12.30 Networking and Lunch
14.30 – 15.30 Networking Break

Tuesday, 14 October 09.30 – 16.00

09.30 – 10.15 Networking Break
14.30 – 15.30 Networking Break

Wednesday, 15 October 09.15 – 11.00

09.15 – 11.00 Closing Brunch

Training

Practical Application of Technology Transfer (T19)

New Course and Guide

Dates: 14 - 15 Oct 2014
Instructor: Bruce S. Davis, Principal, Global Consulting
Level: Intermediate *ISPE CEUs:* 1.3

Technology transfer (TT) includes knowledge transfer, science and risk-based principles including ICH Q8, Q9, Q10, Q11 and efficient processes to meet evolving business needs. As the industry continues to experience changes, technology transfer for active pharmaceutical ingredients (APIs), finished dosage forms and analytical methods between development and manufacturing sites and contract manufacturing organizations (CMOs) has become increasingly important. This course identifies criteria for successful TT and provides "how to" examples which can be individually tailored, depending on the type and scope of transfer. It takes into account current industry challenges and real-world examples as tools for industry and regulators to use when conducting and evaluating technology transfer activities.

Architects, Engineers, Constructors

CRB, 7410 N.W. Tiffany Springs Pkwy., Ste. 100, Kansas City, MO 64153. (816) 880-9800. See our ad in this issue.

EI Associates, 8 Ridgedale Avenue, Cedar Knolls, NJ 07927. (973) 775-7777. See our ad in this issue.

Pharmadule Morimatsu AB, DanvikCenter 28, SE – 13130 Nacka, Sweden. +46 (0)8 587 42 000. See our ad in this issue.

RPA Engineering, 2541 General Armistead Avenue, Suite 100, Norristown, PA 19403. (484) 681-9170. See our ad in this issue.

Stantec, 111 Grant Ave., Suite 201, Endicott, NY 13760. (607) 321-6148. See our ad this issue.

Consulting

PharmEng Technology, 2501 Blue Ridge Road, Suite 250, Raleigh, NC 27607. (416) 385-3922. See our ad in this issue.

Dust Collection Systems and Equipment

Camfil Air Pollution Control, 3505 S. Airport Dr., Jonesboro, AR 72401. (870) 933-8048. See our ad in this issue.

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Electropolishing

UltraClean Electropolish, Inc., 1814 Sunny Dr., Houston, TX 77093. (877) 823-7911. See our ad in this issue.

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Valsteam, Rua da Guia, 3105-467, Guia PBL, Portugal, +351 236 959 060. See our ad in this issue.

Filling and Packaging Equipment

Robert Bosch Packaging Technology, 8700 Wyoming Ave. N., Brooklyn Park, MN 55445. (763) 424-4700. See our ad in this issue.

Instrumentation

Endress+Hauser, Kägenstrasse 2, 4153 Reinach, Switzerland. +41 61 715 75 75. See our ad in this issue.

Particle Measuring Systems Inc., 5475 Airport Blvd., Boulder, CO 80301. (303) 443-7100. See our ad in this issue.

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AAF International, 9920 Corporate Campus Dr., Ste. 2200, Louisville, KY 40223. (502) 637-0320. See our ad in this issue.

Information Technology

COPA-DATA GmbH, Karolingerstrasse 7b, Salzburg, Austria 5020. +43 662 43 10 02-0. See our ad in this issue.

Instrumentation

Bürkert Fluid Control Systems, Christian-Bürkert-Strasse 13-17, D-74653 Ingelfingen, Germany. +49 (0)7940 10 0. See our ad in this issue.

Process Engineering

Sartorius Stedim Biotech (USA), 5 Orville Dr., Suite 200, Bohemia, NY 11716. (800) 635-2906. See our ad in this issue.

Sturtevant, Inc., 348 Circuit St., Hanover, MA 02339. (781) 829-6501. See our ad in this issue.

Process Measurements and Control Systems

Finesse Solutions, LLC, 3501 Leonard Ct., Santa Clara, CA 95054. (408) 570-9000. See our ad in this issue.

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classified advertising

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Pumps

Alfa Laval, Inc., 5400 International Trade Dr., Richmond, VA 23231. (804) 222-5300. See our ad in this issue.

Fristam Pumps USA, 2410 Parview Rd., Middleton, WI 53562. (800) 841-5001. See our ad in this issue.

Software Simulation and Processing Systems

Intelligen, Inc., 2326 Morse Ave., Scotch Plains, NJ 07076. (908) 654-0088. See our ad in this issue.

Validation Services

Azzur Group, LLC, 726 Fitzwatertown Rd., Ste. 6, Willow Grove, PA 19090. (215) 322-8322. See our ad in this issue.

Commissioning Agents, Inc., 652 N. Girls School Rd., Indianapolis, IN 46214. (317) 271-6082. See our ad in this issue.

Emerson Process Management, 8000 W. Florissant Ave., St. Louis, MO 63136. (314) 553-2000. See our ad in this issue.

ProPharma Group, Inc., 10975 Benson Drive., Ste. 330, Corporate Woods Bldg. 12, Overland Park, KS 66210. (913) 661-1662. See our ad in the issue.

Water/Steam Systems

Biopharmax Ltd, 4 Hasadnaot Street, Herzlia, Israel 46728, +972-9-9716116. See our ad in this issue.

Water Treatment and Purification

ELETTRACQUA Srl, Via Adamoli 513, 16165 Genoa, Italy. +39 010 8300014. See our ad in this issue.

Mettler-Toledo Thornton Inc., 36 Middlesex Turnpike, Bedford, MA 01730. (800) 510-7873. See our ad in this issue.

Swan Analytical USA, 225 Larkin Drive Unit 4, Wheeling, IL 60090. (847) 229-1290. See our ad in this issue.

advertiser's index

Time to Cast Your Vote in the 2014 – 2015 International Board of Directors Election

As an ISPE Member, you have the opportunity to choose representatives to fill open seats on ISPE's International Board of Directors. The Board creates the Society's vision, establishes or approves Society policies and controls Society business. It's an important job!

Look for your electronic ballot via email* in late July and cast your vote by 21 August 2014.

Questions? Email Susan Obarski at sobarski@ISPE.org or call +1-813-960-2105 ext. 222.

*Email will be sent by Intelliscan, Inc., our independent outside election partner. Please add @intelliscaninc.net to your "safe senders" list to ensure you receive your official email ballot. If we do not have your email address on file, you will receive a postcard with voting instructions.

Record performance is standard

Long-term business health is less about breaking records than it is about keeping them. That's why we're introducing a new documentation package for our extensive range of biopharm pumps. Q-doc gives complete peace of mind, from sourcing and installation, to validation and operation. Material certificates cover all wetted product parts, including elastomers and spare parts. Naturally our pumps are purpose built for the demands of the industry, featuring exceptional cleanability and high energy efficiency. For certainty, choose a pump with documented performance.

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Rotary lobe pumps