This article offers an alternative method to cleaning validation using online total organic carbon analyzers to determine cleaning validation in-situ. Methods are compared with traditional laboratory analysis.

Online Total Organic Carbon (TOC) as a Process Analytical Technology for Cleaning Validation Risk Management

by Keith Bader, John Hyde, Peter Watler, and Amber Lane

Online Total Organic Carbon (TOC) analysis has progressed significantly in the past few years, yet it remains an under-utilized technology. The US FDA has stated that TOC is an acceptable method for both cleaning validation and routine monitoring, provided the suitability of the method has been established and documented.[1] Advances in TOC analyzer oxidation and analysis methodologies make their integration into Clean-in-Place (CIP) systems instrumentation relatively easy as a means to provide near real time cleaning process performance information. While it is currently possible and practical to utilize online TOC analysis for the real-time assessment of CIP cycle performance, the biopharmaceutical manufacturing industry has been slow to adopt it without favorable and accepted regulatory precedents. However, these precedents do exist in FDA guidance documents on Process Analytical Technology (PAT), the Risk-Based Manufacture of Pharmaceutical Products (both in 2004), and the International Conference on Harmonization (ICH) Quality Risk Management guideline in 2005, which signal a regulatory environment receptive to active monitoring and control of critical process parameters.

The case study presented in this article was conducted to test the relative cleanability of three different bottom mounted agitators. The data by which the cleaning process was evaluated was acquired using an online TOC analyzer integrated into the return line of a CIP system as well as by conventional manual indirect and direct sampling and offline analysis.

Implementing TOC as an online process analytical technology requires first determining if the analytical technology and method are appropriate for the application. Primarily, the installation of process analyzers on equipment used in GMP manufacturing facilities should be done only after risk analyses are performed to ensure that the installation does not adversely affect the process or product quality. The location, physical integration, and automation of the online analyzer into the cleaning system return piping are important considerations as these factors may impact the accuracy and robustness of the measurements. Once installed, the reliability of the technology must be demonstrated through a comparison of online results with existing conventional test methods, including any developmental studies supporting the efficacy and appropriateness of the particular analytical method. In this case, the analytical method TOC, is used to detect process and product residues in final rinse water following cleaning.

Selection of a TOC Analyzer Based on Instrumental Characteristics and CIP Process Considerations

The selection of an appropriate TOC analyzer requires knowledge of its basic operating principles to ensure that CIP process conditions do not interfere with analytical results. Since there is little opportunity to customize the available features of an online TOC analyzer, selection of an analyzer with the appropriate oxidation and sensor equipment can accommodate both analyzer specifications and CIP operational requirements. Though the basic operational principles for all TOC analyzers are much the same, the oxidation and sensor technologies vary between manufacturers. Matching the character-

Continued on page 10.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2009,
Vol. 29 No. 1

Innovation
makes it possible

Telstar Life Science solutions is constantly innovating to offer tailor-made solutions in high technology equipment for the pharmaceutical, biotech and related industries.

With over 45 years of experience and an international presence in more than 100 countries, Telstar is your partner to provide solutions in the following technologies:

Telstar ACE

High Containment Isolators

Telstar Celester

Sterilization Systems, WFI & Pharmaceutical Steam Generation Systems

Telstar Lyo

Freeze Drying Systems

Containment Systems
- Isolators
- Restricted Access Barrier Systems (RABS)
- Downflow booths

Sterilization Systems
- Moist heat sterilization autoclaves
- Chemical agent sterilization autoclaves
- Sterilization and depyrogenation ovens

WFI & Pharmaceutical Steam Generation Systems
- Multiple/simple effects stills
- Pure steam generators

Freeze Drying Systems
- GMP production freeze dryers
- Laboratory freeze dryers
- Loading & unloading systems

Laminar Air Flow Systems
- Laminar flow benches
- Biosafety cabinets
- Laminar flow booths
- Customized cabinets

Drying Systems
- Hot air drying
- Vacuum drying

Telstar®
Life Science solutions

TELSTAR LIFE SCIENCES
Josep Tapioles 120
08226 Terrassa (Spain)
T. +34 937 361 600
F. +34 937 859 342
sales.pharma@telstar.eu

TELSTAR NORTH AMERICA
1504 Grundy's Lane,
Bristol, PA 19007 (USA)
T. +1 215 826 0770
F. +1 215 826 0222
telstar.na@telstar.eu

www.telstar-lifesciences.com

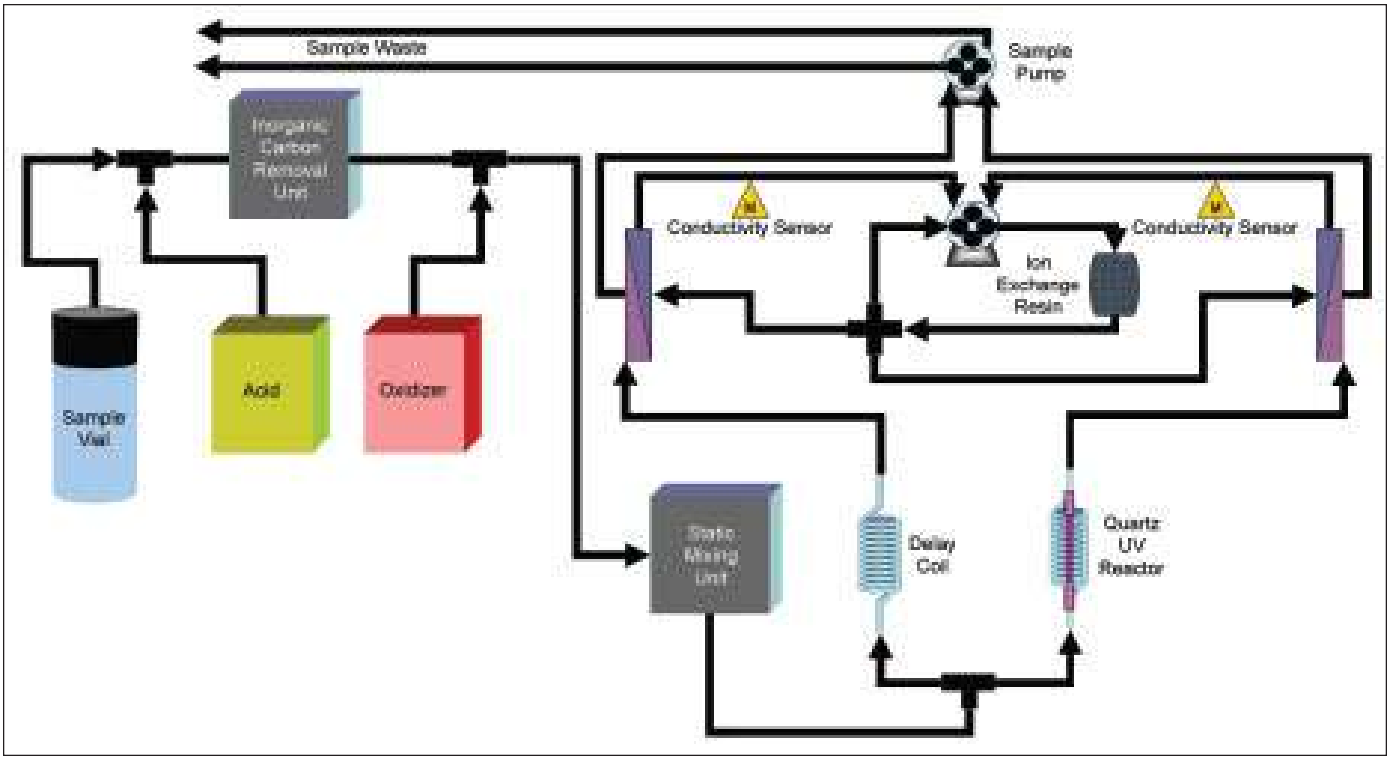


Figure 1. Diagram of a membrane conductometric UV/persulfate TOC analyzer - optional inorganic carbon removal units may be employed if samples have higher levels of dissolved atmospheric CO_2.

istics of CIP processes with an array of specific sensor and oxidation technologies compatible with those characteristics will yield a robust application of the online analyzer, enabling minimized operational and validation efforts with respect to cleaning processes.

For CIP applications, accurate results from an online analyzer must not be confounded by interference from ionic species, variations in sample pressure, or changes in sample temperature. Since conductivity is used in some cases to quantify evolved CO_2, the ionic species in many cleaning agent formulations must be considered as a potential source of interference. These conductive species may be addressed through the use of a membrane conductometric sensor as in Figure 1 or through the use of photometric detection schemes that are insensitive to the presence of conductive ions. Membrane conductometric detectors allow selective permeability of CO_2 across a membrane without permitting other conductive ions into the measurement zone. Therefore, measured conductivity results entirely from Inorganic Carbon (IC) or Total Carbon (TC) oxidized to CO_2, effectively eliminating this source of interference.

For online TOC analyzers in which samples are directly introduced to the analyzer from the CIP return manifold, sample temperature and pressure are relevant parameters to consider. Sufficient pressure is required in the sample line to ensure that the analyzed sample concentration doesn't significantly lag in the CIP return piping. Additionally, care also should be taken to protect the analyzer from pressures exceeding manufacturer's recommendations. In most cases, CIP pressures will not exceed the pressure specifications for an instrument; however, close attention must still be given to the configuration, size, and placement of automated sampling valves and associated sample lines drawing from CIP system return lines. Stabilization of analyzer inlet pressure and flowrate will allow for consistency in the residence time of fluid in the sample lines.

Temperature fluctuations are a relevant concern depending on the selected analyzer, especially if the analysis method is conductometric. Conductivity is a temperature dependant measurement that each instrument manufacturer accommodates in a different manner. Temperature variations in the sample stream may be addressed through temperature compensated conductivity sensors, or measurement of raw conductivity data with sampling apparatus that allow for temperature equilibration through ambient dissipation or active heat exchange. Alternatively, a detection method that is not temperature dependant (such as NDIR) may be used.

TOC concentration is indirectly obtained by calculating the difference between two directly measured parameters; TC and IC. Equation 1 illustrates this relationship.

$$TOC = TC - IC \qquad \text{(Eq1)}$$

Total Carbon is determined by oxidizing organic carbon containing compounds to CO_2 and quantifying both the inorganic carbon already present in the sample along with the evolved CO_2. In the case of a membrane conductometric analyzer (Figure 1), Inorganic Carbon (IC) in analyzed samples results from dissolved CO_2 species (HCO_3^-, CO_3^{-2}), and may be measured directly without oxidation of the sample.

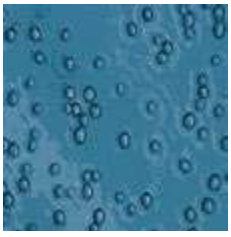
As depicted in Figure 1, solution from the sample vial is injected into the analyzer where acid is introduced to the

Continued on page 12.

GEA Niro Soavi Laboratory Homogenizer

type PANDA™ 2K 1001L

The PANDA™ NS1001 2K is a bench top unit capable of handling a broad range of applications including cell rupture, particle size reduction and emulsions. The PANDA™ 2K with its small hold-up volume and flow rate is ideal for processing small batches of product with results that are directly scalable through to pilot and production machines operating at up to 5500 l/h.



Before

After

PANDA™ NS1001 2K Specifications and Performance:

- Operating pressure 0 – 1500 bar
- Flow rate up to 12 l/h @ 1500 bar
- Minimum sample volume 200ml
- Maximum product viscosity 2000 cPs (20,000 with optional pressure feed)
- Maximum inlet particle size = 0.5mm
- Optional 2nd stage homogenizing valve
- Suitable for CIP and SIP
- ½" Tri Clamp inlet/outlet connections
- Dimensions – L800mm x W460mm x H420mm
- Weight – 85 kg
- 1.8 kW 3ph/60Hz/ 208, 230 or 460V motor (only utility requirement)
- Optional inverter available to allow 1ph/ 60Hz/200-240V power supply

Engineering Excellence.

Process Engineering

GEA Liquid Processing

GEA Process Engineering Inc. • 9165 Rumsey Road • Columbia MD 21045
Tel: 410 997 8700 • Fax: 410 997 5021
E-mail: info@niroinc.com • Website: www.niroinc.com

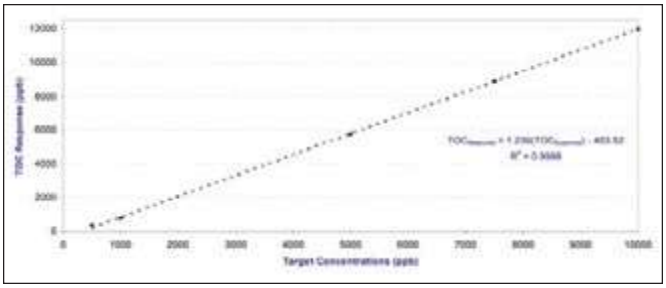


Figure 2. TOC response curve for Bovine Serum Albumin.

sample stream. The added acid shifts the equilibrium such that inorganic carbon species convert to CO_2. After the acid addition, a persulfate oxidant is added and the sample stream mixed to ensure homogeneity. The sample stream is then split with one stream passing through a reactor and exposed to UV light, initiating a photolysis reaction. As the sample in the reactor is oxidized, CO_2 evolves and is transferred across a gas permeable membrane into a deionized water stream where its conductivity is measured. The formation of the conductive species occurs via the carbonate buffer pathway shown in Equation 2.

$$CO_2 + H_2O \leftrightarrow H_2CO_3$$
$$H_2CO_3 + H_2O \leftrightarrow H_3O^+ + HCO_3^- \quad \text{(Eq2)}$$
$$HCO_3^- + H_2O \leftrightarrow H_3O^+ + CO_3^{-2}$$

The other sample stream flows through a hydro-dynamically identical path (identified in Figure 1 as the delay coil) where dissolved CO_2 is transferred across the membrane and conductivity is measured to provide an inorganic carbon reference measurement required for the calculation of TOC.

Analytical and Sampling Method Development

For this study, two analyzers were employed; both equipped with membrane conductometric sensors. The offline analyzer used a methodology based upon UV and persulfate oxidation, whereas the online analyzer used only UV oxidation. To ensure the reliability and comparability of the measurements from the online and offline analyzers, USP system suitability tests were preformed to confirm response efficiency using 1,4 benzoquinone and sucrose standards. The instrumental limit of detection of 50 ppb TOC required per the USP[2] was met for both analyzers.

Once operation of both analyzers was demonstrated to be acceptable, methods were developed using the offline analyzer to characterize the Bovine Serum Albumin (BSA) to be used as a representative process soil and to evaluate and quantify the systemic and experimental error associated with TOC surface swab sampling. Stainless steel coupons also were spiked at multiple weight loadings to develop a recovery response curve.

From a 10% by weight solution of BSA, a series of dilutions were prepared with target concentrations of 500, 1000, 5000, 7500, and 10,000 ppb TOC. The solutions were then analyzed to ensure that the TOC response curve for BSA was linear and to empirically characterize the samples' carbon content to establish a correlation between the concentrations of TOC and BSA.

Analysis of the samples produced the response curve shown in Figure 2. Also reported are the linear regression trend line through the data points, which provides an indication of the linearity of the relationship, Limits of Detection (LOD) and Limits of Quantitation (LOQ). The regression line correlation coefficient (R^2) of 0.9998 demonstrates that the regression line fits the data and is a reasonable model for the plotted data.

To ascertain the surface swab recovery characteristics for BSA, a study was conducted using stainless steel coupons spiked with known concentrations of BSA. The target organic carbon loading (ppb) is indicated by the Sample ID numbers in Table A. To account for the inter-individual variability, the study was conducted with three technicians independently executing the swab sampling method. Swab sampling recovery was evaluated by comparing the TOC recovered from the coupons to the TOC content of positive control samples in which equivalent amounts of BSA solution to that spiked on the surface of the corresponding coupons was spiked into a vial containing 40mL of diluent. The results are summarized in Table A, and shown graphically in Figure 3 and Figure 4.

The correlation coefficient (R^2) value greater than 0.99 for each of the technicians provides assurance that the recovery fits a linear model when inter-individual variability is taken into account. Evaluation of the LOD and LOQ for the sampling method for each technician is shown in Table A and ranges from 122 to 195 ppb TOC, and 371 to 589 ppb TOC, respectively. The slope of each recovery curve also is a representation of the overall surface swab recovery over the

Sampling Technician	Sample ID	Positive Control TOC (ppb)	Blank Corrected Sample TOC (ppb)	Percent Recovery	Sampler LOD	Sampler LOQ
1	250	231	181	78.5	125	377
	500	633	594	93.8		
	1000	1137	1016	89.3		
2	250	231	194	84.1	122	371
	500	633	561	88.5		
	1000	1137	936	82.3		
3	250	280	193	68.8	195	589
	500	808	649	80.2		
	1000	1105	1017	92.0		

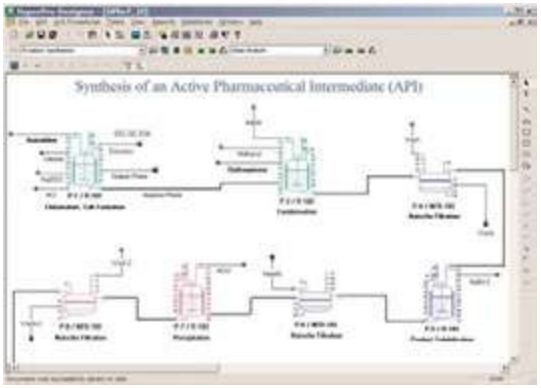
Table A. Surface swab recovery results.

Continued on page 14.

Intelligen Suite

The Market-Leading Engineering Suite for Modeling, Evaluation, Scheduling, and Debottlenecking of Single & Multi-Product Facilities

SuperPro

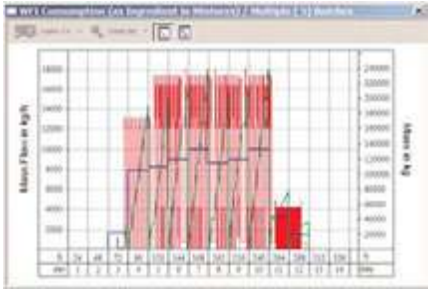


Use SuperPro Designer to model, evaluate, and debottleneck batch and continuous processes

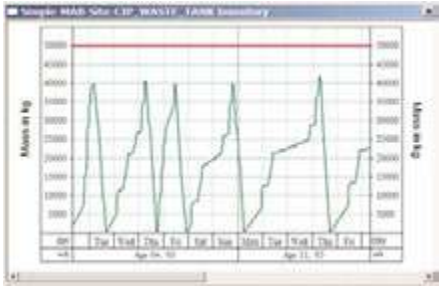
SchedulePro

Switch to SchedulePro to schedule, model, and debottleneck multi-product facilities

Tracking of equipment occupancy in multi-product facilities



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



Inventory tracking for raw materials, intermediates, products, and wastes

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of biochemical, specialty chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 400 companies and 500 universities around the world (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

SchedulePro is a versatile finite capacity scheduling tool that generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of facilities, equipment, resources and work areas. 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 utilities for batch plants, identify equipment requirements, reduce cycle times, and debottleneck facilities.

Visit our website to download detailed product literature and functional evaluation versions of our tools

INTELLIGEN, INC. • 2326 Morse Avenue • Scotch Plains, NJ 07076 • USA
Tel: (908) 654-0088 • Fax: (908) 654-3866
Email: info@intelligen.com • Website: www.intelligen.com
Intelligen also has offices in Europe and representatives in countries around the world

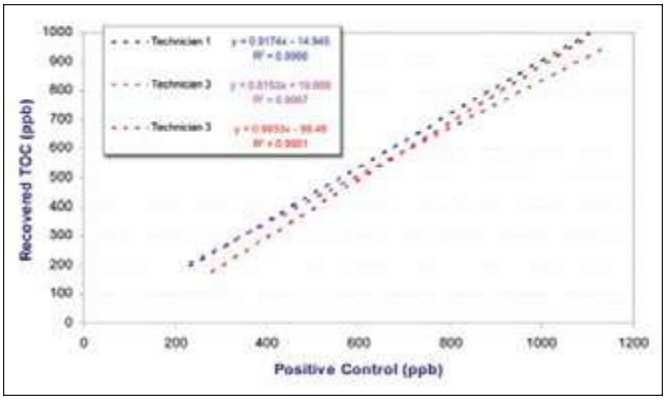


Figure 3. Individual technician swab recovery results.

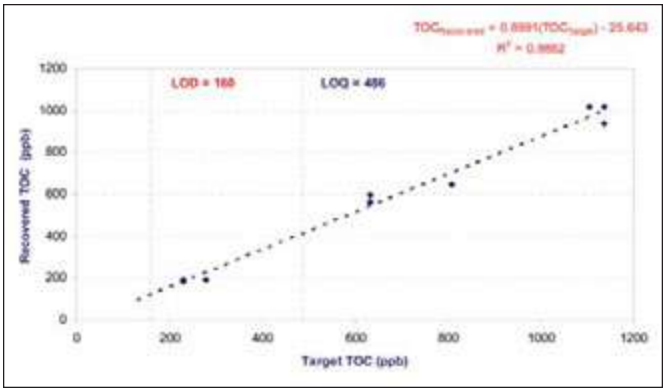


Figure 4. Characterization of TOC surface swab sampling method (BSA swab recovery [aggregate]).

Sampling Method	LOD(ppb TOC)	LOQ(ppb TOC)
Swab	161	486

Table B. Sampling method limits.

range of the indication that on average, each of the technicians will, at a minimum, likely recover greater than 80% of BSA residues remaining on process surfaces within the tested range.

The slope of each line shown in Figure 3 indicates the overall recovery across several residue loadings for each technician. Additionally, relative standard deviation of the individual recovery results was used as the primary statistic of interest to assess the precision of the results and the reliability of the data for each individual technician. Reviewing the discrete relative standard deviation numbers and the R^2 values for each technician, some variability is expected and was apparent.

Intuitively, pooling the data for all of the technicians should create a model incorporating inherent systemic error as well as that resulting from inter-individual variability. To confirm this hypothesis, a t-test conducted for the three data sets confirms that the sample sets for all the technicians may be pooled since they are statistically similar with a high probability of sharing the same sample mean.

Linear regression statistics for the response curve, as well as LOD and LOQ were determined. The LOD and LOQ are evaluated through the following equations:

$$LOD = \frac{3.3s}{m} \quad \text{(Eq3)}$$

$$LOQ = \frac{10s}{m} \quad \text{(Eq4)}$$

In Equations 3 and 4 above, ***s*** defines the standard deviation from the calibration curve and ***m*** the slope of the regression line.[3] However, the quantity, ***s***, may be determined multiple ways: from the standard deviation of the regression line, the standard deviation of y-intercepts of the regression line, and the standard deviation of an appropriate number of blank responses.

The pooled data for all the technicians is represented graphically in Figure 4, and shows an overall recovery of approximately 90% with a correlation coefficient of 0.986, and aggregate limits of detection and quantitation of 160 and 486 ppb TOC.

As noted above, an alternative method for estimating the LOD is to use the average of the swab results from the swabbing of 10 clean stainless steel coupons. This will quantify the approximate background levels resulting from the water, vials, swabs, and other random experimental sources. The average TOC from the swabbing of 10 clean stainless steel coupons was 161 ppb with a relative standard deviation of 9.3%. Accordingly, the LOD values determined by the two methods were nearly identical.

Using TOC swab LOQ as the limit for passing cleaning results, values in excess the TOC swab LOD were evaluated to determine a root cause for the failure. Corroboration of the online and offline rinse samples also was considered in the analysis.

Cleaning Study Results

The CIP test system depicted in Figure 5 was used to compare the cleanability of three bottom mounted agitators of differing design. The components that comprise the CIP test system include a water supply tank, a heat exchanger, automated valves, Variable Frequency Drive (VFD) controlled pumps,

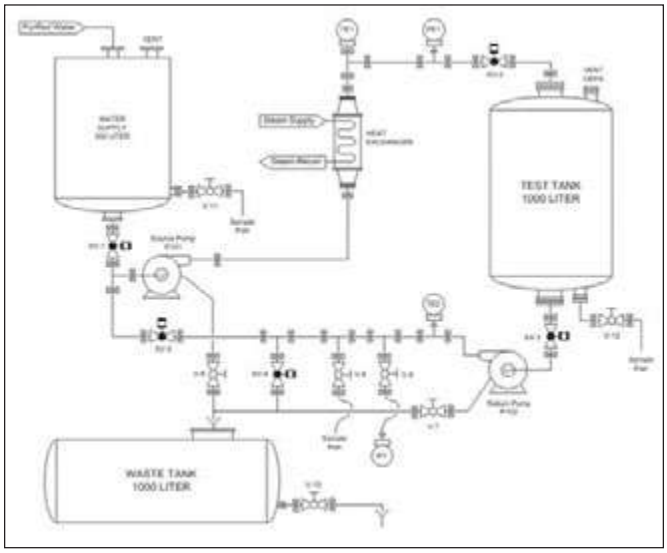


Figure 5. Schematic of CIP skid with online TOC analyzer.

Continued on page 16.

Sharing the value of our combined expertise

Today Edwards Pharmaceutical Systems is part of IMA Group

The best in freeze-drying technology, hand-in-hand with the world's leading name in one stop aseptic processing and filling solutions for the pharmaceutical industry.

At IMA, we are dedicated to building strong client relationships and strive to offer solutions which guarantee efficiency and competitiveness in the global pharmaceutical market.

That is why we have fully integrated Edwards's lyophilisation systems and expertise in order to supply the pharmaceutical industry with even more advanced and complete aseptic processing and filling lines.

IMA LIFE S.r.l.
mktg.filling@ima.it • www.ima.it
IMA EDWARDS
sales@imaedwards.com - services@imaedwards.com • www.imaedwards.com

IMA EDWARDS
Freeze Drying Solutions

IMA LIFE SOLUTIONS: VIAL LOADING • WASHING • DEPYROGENATING • FILLING • FREEZE-DRYING • STOPPERING • CAPPING

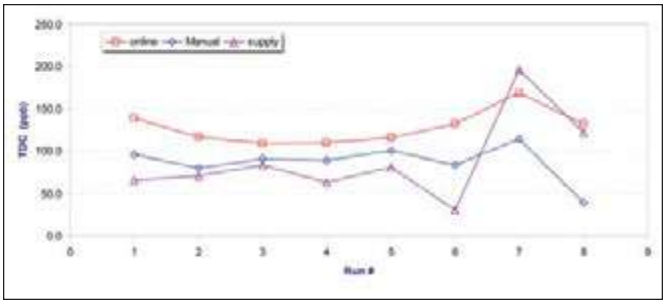


Figure 6. Comparison of manual and online TOC rinse samples.

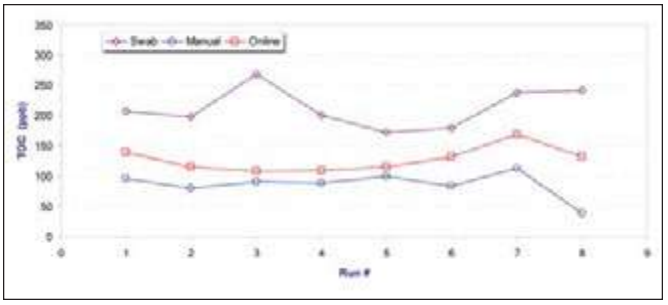


Figure 7. Comparison of online to direct and indirect sampling method results.

and a 1000L vessel in which the agitators were installed for testing. The critical parameters of temperature and flow rate were controlled via PID controllers, along with carefully controlled circuit fill volumes and detergent concentrations to ensure uniform reproducible operations for each run.

To asses each run, final rinse water samples were taken online through the TOC analyzer sample line located at valve V-8. The TOC analyzer is represented in the drawing as analog input signal AI-1. All manual samples taken for comparison were drawn from valve V-9, which was located immediately adjacent to the TOC analyzer sample line. To provide a point of reference for each run, the supply water was manually sampled from V-11. The agitators were each installed in the tank in analogous positions and, as noted before, subjected to the same cleaning procedure and parameters.

To soil the equipment, BSA was manually applied to the internal tank surfaces as well as the entirety of each agitator and allowed to dry. Once dry, the CIP cycle was initiated, consisting of an initial rinse, an alkaline wash, an intermediate rinse, an acidified wash, and purified water final rinses. For each cycle, Steris CIP-100, at 1% concentration by volume, was the cleaning agent used for the alkaline wash. The cleaning agent used for the acidic wash solution was 1% by weight phosphoric acid. The acid wash cycle was then followed by a once-through rinse and a subsequent recirculated rinse. Since the online analyzer required a brief equilibration period before it was ready to sample, the second final rinse was recirculated as once-through rinse durations were inadequate for the analyzer to complete its start up cycle.

Just before completion of the cleaning cycle, manual samples were taken at the beginning of the final rinse recirculation. After completion of the cleaning cycle, manually acquired rinse and swab samples were taken for comparison with those from the online TOC analyzer.

Comparability of the sampling and analytical methods was assessed through analysis of the manual and the online results. These data are shown in Figure 6. The online results also were compared to TOC surface swab samples to any correlation between the methods.

Correlation of the results of all three methods is apparent with the most notable event being the results from run 7. The supply water was accidentally contaminated by overfilling the flat topped supply tank, transferring contaminants from the lid and seal of the vessel into the bulk solution. In each case, the sampling methods detected the excursion.

The comparative results for the surface swab samples are shown in Figure 7. The general trend is the same for the surface swab samples with the exception of run 3 in which the surface swab results are higher than either the manual or online rinse samples. This may have been due to inadequate surface cleaning of BSA residue that was not completely soluble in the final rinse water.

The data from all runs demonstrates that rinse samples, whether online or manual, do provide a good indication of the residue levels on the equipment surfaces with the absolute TOC value difference between swab and rinse samples being attributed to the added TOC background inherent to the swabbing method.

Another interesting observation is the fact that the manually collected rinse sample TOC results were lower than those from the online analyzer, while one might expect quite the opposite. The manual samples were taken at the beginning of the recirculated rinse cycle prior to an extended recirculation time. Once the analyzer had completed the initial rinse cycle (approximately 4 ½ minutes), the online samples were taken. The higher results from online TOC samples may be due to the recirculation of the rinse water prior to sampling. Recirculation of final rinse water is a deviation from typical CIP processes, and recirculation causes the rinse water to be directed back through pathways that would not ordinarily have contact with a final once-through rinse. This potentially contributed some TOC to the final rinse results from the additional surface area contacted by the final rinse water.

Another contributing factor to the higher online TOC results is the configuration of the online analyzer sampling piping which is depicted in Figure 8. The illustration approximates the spatial layout of the sampling equipment. The TOC analyzer sample valve, XV-8, was oriented downward, and did not have an additional drain or flush valve to remove solution from the lines. The manual rinse sampling valve, on the other hand, was flushed prior to sample collection per the procedure for the sampling method, clearing any residue from the sample path that could contribute to elevated TOC levels.

This principle of rinsing the path prior to sample collection and analysis may be incorporated into the sampling arrangement for the analyzer to allow for clearance of residues prior to sample collection. An example of a possible piping configuration to minimize process residue retention is shown in Figure 9. In this arrangement, the sample line branches from the process line such that the inlet to the line is constantly

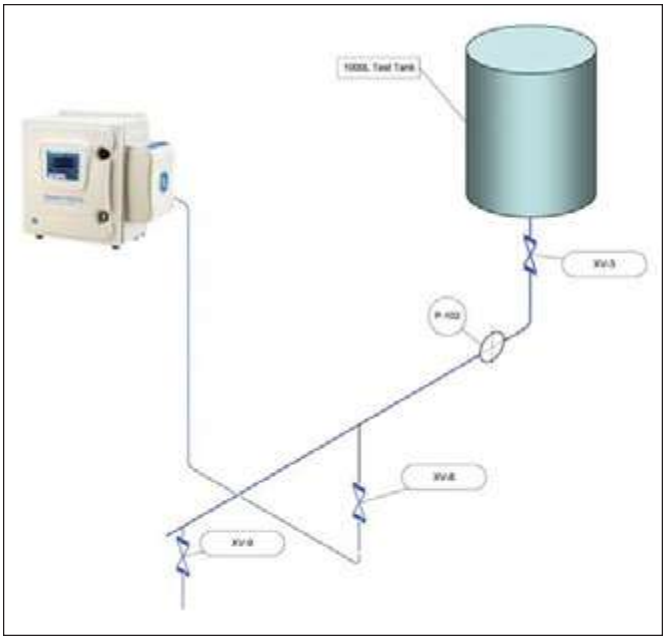


Figure 8. Isometric layout of sampling equipment.

swept clear by the process fluid. Further, the installation of a drain valve is useful to allow for flushing of the line prior to sampling, as well as draining the sample line after sampling is completed. Sloping the sample line back to the drain valve also will minimize retention of process fluid from previous sampling operations.

Conclusions

The cleaning of pharmaceutical manufacturing equipment systems by automated Clean-in-Place (CIP) means has long provided superior reliability and consistency as compared to manual cleaning operations that are subject to human error. Through the introduction of more reliable and affordable sensor technologies, including advances in online TOC technology, the cleaning process can be very effectively controlled and monitored by removing variability inherent to manual collection and analysis of cleaning verification and validation samples. Accordingly, implementation of TOC as a process analytical technology for cleaning systems can improve knowledge and control of the cleaning process beyond real time

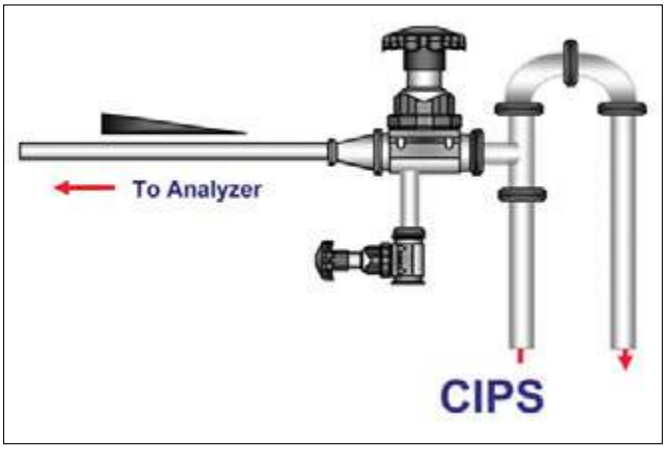


Figure 9. Online analyzer sampling configuration.

Continued on page 18.

awareness of final rinse water quality at a discrete moment in time. The combination of online TOC and online conductivity measurements provides a means for real-time verification of cleaning cycle performance, and using statistical process control methodologies, ongoing analysis of the consistency of critical control parameters and quality attributes for the cleaning process. This ongoing monitoring can provide the basis for evaluating drift and the need for re-qualification based upon events rather than elapsed time. The data from ongoing monitoring also can provide a foundation for cleaning validation that is not based upon a model of three passing commercial scale runs, but rather a model that uses evidence from cleaning cycle performance, on an every run basis, to provide assurance of successful operations prior to the manufacture of each production run.

The implementation of online TOC sampling and analysis must be done by carefully selecting an analyzer that is compatible with the cleaning process and subsequently installing it such that the results are truly representative of TOC levels in final rinse streams. The selected TOC analyzer must be able to tolerate conductive ions such as those present in cleaning agents. The analyzer also must be able to tolerate, and depending on the intended use, analyze occasional spikes of TOC greater than 1 – 2 ppm. This study has demonstrated that an advanced oxidation differential conductivity membrane sensor based instrument is suitable for online CIP rinse water analysis. Other technologies may be suitable based on the specific requirements of the application. If the analyzer will not be used for an application in which conductive ions are present and TOC concentrations are rarely in excess of 2 ppm, it may be possible to use an advanced oxidation based instrument that measures TOC through the use of direct conductivity. For concentrations of TOC in excess of 2 ppm with the possibility of conductive ions, end users may wish to consider the use of a UV persulfate oxidation system with an NDIR or differential membrane conductivity sensor.

Additionally, the sample equipment on the CIP system should be configured to deliver solution to the analyzer quickly without carryover from run to run. This is best accomplished by ensuring a short residence time with adequate turbulence in fully drainable sample lines for complete removal of fluid when the equipment is not in use. Once qualified, the TOC analyzer can identify trends predictive of adverse events or inadequate process control, allowing for timely application of corrective measures. This utilization of real time cleaning process performance information will yield product quality and economic benefits.

To gain regulatory acceptance for the utilization of online TOC analysis for ongoing monitoring of cleaning efficacy, the instrumentation and method must be qualified in a manner consistent with offline validated and compendial sampling and analytical methods. Further, implementation of online TOC sampling and analysis as a component of a PAT strategy for cleaning processes is only practical if the results are equivalent or better than those attained from existing methods. This may be done by comparing the results obtained using both methods and modifying the sampling equipment configuration to ensure that the online methodology is accurate and robust, and at the very least, equivalent to the results of offline sampling methods.

Although some have suggested that online TOC measurement provides additional liability should TOC levels exceed acceptance limits in final rinse water, online TOC measurement compliments and enhances the level of process knowledge from which critical process decisions may be made. Typically, once a system has been validated, TOC rinse samples are not taken for every run unless necessitated by poor system performance or a philosophy that embraces an extremely low risk tolerance. CIP systems often rely on monitoring and control of critical process control parameters, measured by temperature, flow rate, and conductivity sensors in the appropriate locations[12] to ensure that cleaning cycles operate within established and validated ranges. While this approach effectively takes care of the input side of the cleaning process, final rinse water TOC, which is a critical quality attribute for cleaning, has not typically been addressed. Online final rinse water and TOC data will provide more complete information from which to assess the efficacy of cleaning operations on an every run basis, yielding comprehensive and ongoing control well beyond the current status quo.

The monitoring and control of critical quality attributes for cleaning operations offer further economic and quality benefits in reduction or elimination of cleaning related OOSs and their associated investigations and resolutions. These cost reductions can be realized not only through more efficient processes that facilitate faster and more flexible production schedules, but also through the minimization of labor hours invested in manual operations required to support systems, through manual sampling and analysis, which cannot provide the same sensor based process control information. In many manufacturing facilities, cleaning validation samples are manually collected and submitted for analysis to Quality Control laboratories, or in some cases to off-site contract analytical laboratories. These activities involve both time and expense for the manufacturer in the form of labor hours for collection of the data, sample collection materials, time and resources of the QC laboratories, and opportunity cost related to delays in manufacturing operations from waiting for analytical results to determine if cleaning processes were successful.

Finally, the economic benefits of online sampling are supported by the time recorded in the execution of this study to conduct the manual sampling and analysis as compared to the time investment required for running the online analyzer during CIP operations. The time required for the collection preparation and analysis of the samples collected for nine cleaning runs was in excess of 80 labor hours. In contrast, the total set up time for the online analyzer was approximately three labor hours. On a per-run basis, preparations for online analysis and sampling required approximately 20 minutes. In comparison, each run required nearly 10 hours of labor for manual sample collection and analysis. Clearly, extrapolating this time savings over the period of a year indicates that

significant savings may be realized, the magnitude of which depends on the particular facility and the number of cleaning operations to be qualified and monitored. Although integrating online TOC measurements into CIP system automation will result in added capital costs, operating costs can be significantly reduced and will likely justify the investment.

Summary

Sophisticated measurement and control strategies have been successfully applied to CIP systems and operations for many years. The utilization of online TOC measurement represents a significant step forward in assurance of product quality and safety through more effective real-time monitoring and control of the cleaning processes. With enhanced quality assurance and reduced cost of goods as driving forces, pharmaceutical manufacturers are automating manufacturing operations to accommodate more complex processes, including more complicated cleaning sequences commensurate with increasingly complex manufacturing equipment configurations and production methodologies. More robust automated systems will provide higher levels of assurance of removal of potential contaminants to acceptable levels. CIP systems can be automated to the point that risk from manual operator actions are eliminated from the process stream, except for manual set-up activities, such as the loading and un-loading of a glass-washer or the starting of a unit operation from a control point.

References

1. US FDA, CDER, "Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance," http://www.fda.gov/cder/guidance/cGMPs/equipment.htm.
2. USP compendial monograph <643>, Total Organic Carbon.
3. Validation of Analytical Procedures: Text and Methodology Q2(R1), International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
4. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Draft Consensus Guideline, Quality Risk Management, Q9," Released for Consultation at Step 2 of the ICH Process on 22 March 2005.
5. Final Report, "Pharmaceutical cGMP for the 21st Century – A Risk-Based Approach," September 2004, http://www.fda.gov./cder/gmp/gmp2004/GMP_finalreport2004.htm.
6. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, "ICH Harmonized Tripartite Guideline, Pharmaceutical Development, Q8," Current Step 4 version dated 10 November 2005.
7. Guidance for Industry, "Development and Use of Risk Minimization Action Plans," March 2005, http://www.fda.

Concludes on page 20.

gov/cder/guidance/6358fnl.htm.
8. Japanese Pharmacopoeial Forum, December 2005, p. 949.
9. Guidance for Industry, "PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance," September 2004, http://www.fda.gov/cder/guidance/6419fnl.htm.
10. Crompton , T. R., **Determination of Organic Compounds in Natural and Treated Waters**, 1st Edition, Taylor and Francis, 29 W. 35th St., New York, NY, 1999, pp. 809-811.
11. Bader, Keith, ASEPCO Mixer Cleaning Study Report, July 26, 2006 http://www.asepco.com/news/.
12. Hyde, John M., Watler, Peter K., and Bader, Keith, "PAT for Pharmaceutical Cleaning," *Control Engineering*, Vol. 54, No. 4, pp. RX1 – RX4, April 2007.

Acknowledgements

The authors gratefully extend their thanks to ASEPCO for their sponsorship of this project and allowing us to share the collected data and to GE Analytical Instruments for the generous loan of online and laboratory TOC analyzers.

About the Authors

Keith Bader is the Director of Technical and Quality Services at Hyde Engineering and Consulting, Inc. As the Director of Technical and Quality Services at Hyde Engineering and Consulting, he is responsible for the implementation of technical and quality documentation and standards for Hyde Engineering and Consulting on a corporate wide basis. Bader also provides high level consultation externally to Hyde Engineering and Consulting's clients in topic areas ranging from strategic quality and validation documentation to design of experiments for supporting studies. He is currently a member of ISPE and American Institute of Chemical Engineers (AIChE), the Parenteral Drug Association (PDA) and has participated with the Society for Bioprocess Professionals (SBP), now a division of ISPE. He holds a BS in chemical engineering from the University of Colorado at Boulder in 1995. He can be reached by email: keith.bader@hyde-ec.com.

John Hyde is the Founder and CEO of Hyde Engineering and Consulting, Inc., which specializes in providing process engineering, commissioning, validation, and FDA compliance services to biopharmaceutical and pharmaceutical manufacturers. Prior to the formation of Hyde Engineering and Consulting, he was a senior project engineer with Synergen, a biophar-maceutical research and manufacturing company located in Boulder, Colorado. From 1982 to 1992, Hyde was manager, Process Systems Design with Seiberling Associates, Inc., an engineering firm specializing in the design and start-up of pharmaceutical, dairy and food process systems and the application of CIP technology. Hyde serves on the board of the Society of Bioprocess Professionals (SBP) and is a regular speaker at conferences presented by SBP, ISPE, PharmaConference, IVT, Microrite, and other professional societies. He holds a BS in food science and business administration, and a Masters in food engineering, all from Ohio State University. He can be contacted by email: John. Hyde@hyde-ec.com.

Peter Watler, PhD is Principal Consultant and Chief Technology Officer with Hyde Engineering and Consulting, Inc. He has 21 years of GMP biopharmaceutical process experience with a focus on process design and scale-up, facility start-up, and validation. He has prepared three license submissions and participated in several FDA inspections and GMP audits. Watler was previously vice president, manufacturing at VaxGen. He led the design, construction, commissioning, and validation of a GMP facility for vaccine production. He also was responsible for managing supply chain and production operations, led the CMC team, and prepared submissions for government agencies. He previously spent 12 years at Amgen, leading process development, manufacturing support, and overseeing pilot plant operations. He led teams for technology transfer, scale-up, pre-clinical production, and process validation for Neupogen®, Stemgen®, Kepivance®, and Infergen®. Walter holds a BS and an MS in chemical engineering from the University of Toronto and a PhD in Chemical Engineering from Yamaguchi University, Japan.

Hyde Engineering and Consulting, Inc., 6260 Lookout Road, Suite 120, Boulder, Colorado 80301, USA.

Amber Lane is currently the Cleaning Validation Specialist for Insmed Therapeutic Proteins, Boulder, Colorado, where she is responsible for the development and implementation of the companies Cleaning Validation programs. She holds a BA in biology with chemistry from Alverno College, Wisconsin. From 2005-2008 Lane was the analytical services manager for Hyde Engineering and Consulting. In that position, she specialized in analytical studies and the development of analytical methods for cleaning validation. She has nine years of experience with TOC analyzer operation, application, design and development, and validation. Prior to working for Hyde Engineering and Consulting, Lane was the technical trainer with Ionics (now GE Analytical), where she was responsible for the design and implementation of training programs for all products, in addition to playing a role in new instrument development. From 1999-2001, she was an analytical chemist with Abbott Laboratories in Illinois. She is currently a member of the American Chemical Society. She can be contacted by email: alane@insmed.com

Insmed Therapeutic Protiens, 2590 Central Avenue Boulder, Colorado 80301, USA.

This article presents the use of visible residue limits. Parameters were defined, their ruggedness determined, and applications described.

Using Visible Residue Limits for Cleaning

by Richard J. Forsyth

Introduction

Before formal cleaning validation programs were instituted, visual inspection was the primary means of determining equipment cleanliness. The use of visual inspection is still typically a component of a cleaning validation program and for routine inspections of cleaning effectiveness. The use of only visual examination to determine equipment cleanliness was proposed as far back as 1989 by Mendenhall.[1] He found that visible cleanliness criteria were more rigid than quantitative calculations and clearly adequate. The FDA, in their "Guide to Inspection of Validation of Cleaning Processes," limited the potential acceptability of a visually clean criterion to use between lots of the same product.[2] LeBlanc also explored the role of visual examination as the sole acceptance criterion for cleaning validation.[3]

The Acceptable Residue Limit (ARL) for drug residue is often determined on a health-based and an adulteration-based criterion.[4,5,6] The limit used is the lower of the two limits. A health-based limit is generated from toxicity data, which can be expressed as Acceptable Daily Intake (ADI). The health-based limit is calculated using the ADI or lowest therapeutic dose and the parameters of the equipment used to manufacture the formulation.[5] For the adulteration limit, a carry-over limit of 10 ppm or a baseline limit of 100 µg/swab is often used in the industry.

Our health-based limit calculation is:

$$ADI/MDD \times DUB/SSA \times M = ARL\ (\mu g/swab)$$

Where: ADI is the Allowable Daily Intake (µg/day) of the residue in question which would have no pharmacologic effect; MDD is the Maximum Daily Dose (units/day) of the subsequent product manufactured in the equipment; DUB is the Dose Units per Batch (units) of the subsequent product; SSA was the Shared Surface Area (cm^2) for the product contact surface area of the manufacturing equipment; M is the swab area (cm^2/swab). Our adulteration-based limit is 100µg/swab.[7] An established visible residue limit, which is below the Acceptable Residue Limit, is a reasonable criterion for cleaning validation.

Visible cleanliness is the absence of any visible residue after cleaning, but a number of factors influence any determination. The most obvious is the observer. Not only the observer's visual acuity, but also training on what to observe, influences the outcome of a visual inspection. The levels of illumination in the inspection areas and shadows caused by the equipment influence what is seen. The distance and the angle of the observer from the equipment surface also have an effect. Finally, the individual residues that comprise a given formulation affect the overall visible residue limit. Jenkins and Vanderwielen observed various residues down to 1.0 µg/cm^2 with the aid of a light source.[4] Fourman and Mullen qualitatively determined a visible limit at approximately 100 µg per 2 × 2 in. swab area[8] or about 4µg/cm^2.

Sample preparation and viewing parameters for VRL use have been established for both pilot plant and commercial manufacturing facilities.[9,10] A solution or suspension of the API applied at different concentrations to stainless steel coupons results in residues of uniform size. Multiple observers determined VRL levels under controlled viewing conditions. The VRL was established at the lowest residue concentration all observers visually detected. A study of viewing parameters, including viewing distance, viewing angle, light intensity, residue composition, and observer subjectivity resulted in optimal viewing conditions to detect

Continued on page 24.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2009,
Vol. 29 No. 1

Important technological advances are brewing in the biopharmaceutical industry…

…and advanced high-purity solutions from MKS are behind many of them.

MKS Instruments, a global leader in critical process management and control, develops and manufactures a wide range of products used in today's most sensitive biotech and biopharmaceutical processes. From instruments to control pressure and flow, to ozone generators for sterilization, to stainless steel fittings, filter housings and housing heaters, MKS has the expertise and cost-effective solutions to address the needs of the most advanced bio processes. For information on these and other MKS products, visit us online at **www.mksinst.com/biopharm.**

mks
Technology for Productivity

MKS Instruments, Inc. Phone: 978.284.4000 or 800.227.8766 (USA only) www.mksinst.com/biopharm

visible residues. Viewing conditions in the pilot plant were set at 18 inches, 30°, and > 200lux. For commercial facilities with larger, fixed equipment, the viewing inspection parameters are more restricted. The optimal viewing conditions for VRLs are ≤ 10feet, ≥ 30°, and > 200lux. A discussion of the applications of VRL use and the associated risks concluded that the potential for a cleaning failure was small under a well controlled VRL program.[11,12,13]

The subjectivity of the observers and the appearance of the dried residues remained as potential limitations to a VRL program. The original VRL work used a small group of four to six observers.[9,10] For subsequent work, a larger pool of observers determined the VRLs of development APIs at one site. In addition, a study of VRL determinations of five APIs at multiple sites helped serve to address the issue of observer subjectivity as well as further define the ruggedness of residue sample preparation. Observers are qualified with a training program consisting of VRL determinations of compounds with already established VRL levels, while emphasizing the importance of residue appearance and viewing parameters.

Applications of VRL use in pilot plant and manufacturing facilities were described.

Visible Residue Parameters

The variables associated with studying visible residue in the pilot plant were defined, and then experimental parameters for the study were established. The parameters considered were: surface material, light intensity, distance, angle, residue appearance, and observer subjectivity.[9]

Stainless steel was an obvious choice for surface material, since >95% of manufacturing equipment surfaces are stainless steel. Representative stainless steel coupons were used for spotting purposes in the laboratory setting.

The lighting conditions in the manufacturing pilot plant differ from room to room. The light intensity was measured in each room of the pilot plant and ranged from 520 – 1400 lux. To allow for shadows and different positions within a given room, it was decided to conduct the visible residue study between 400 and 1400 lux using a light source directly over the sample. A fluorescent light served as a light source to provide the same type of light that is used in the pilot plant. A plastic cover with different degrees of shading was placed over the bulb and was rotated to adjust and control the intensity of the light. A light meter was used to set and verify the various light intensity levels.

To minimize observer subjectivity, a pool of observers viewed all of the samples. A distance of six to 18 inches from the equipment surface and a viewing angle of zero to 90° were considered as practical viewing parameters. A comfortable viewing distance of 12 inches was chosen. A viewing angle of 30° was chosen although lower angles occasionally provided more reflectance. A 30° angle provided the shallowest practical viewing angle, taking into consideration the surface locations where residues are most likely to be seen in manufacturing equipment, i.e., corners and joints.

The lighting conditions in the commercial manufacturing suites differ from room to room and also depend on equipment size and degree of disassembly for cleaning. The larger size of the equipment in the manufacturing facility provided the greatest difference compared to the smaller equipment in the pilot plant. The increased size deepens the shadows in the interior of the equipment. To compensate for lighting conditions, a portable light is used for inspection as necessary. Therefore, the range of lighting for this study was from 100 lux up to the intensity of the portable light. For the lower lighting level, ambient fluorescent light served as a light source to provide the same type of light used in the manufacturing plant. The portable light source was a hand held light. The portable light source was adjusted to maximize viewing conditions. Moving the light source allowed the observer to control the lighting conditions; i.e., optimize the incident light angle and the effect of reflected light on the formulation residue, and minimize the reflecting light back to the observer. A light meter was used to set and verify the various light intensity levels.

The viewing distances for this study were dependent on the size of the equipment. In a commercial manufacturing facility, equipment sizes are larger and viewing distances are greater. Rather than define viewing distances for each piece of equipment, viewing distances were chosen at five, 10, 15, and 20 feet to complement the pilot plant data.

The viewing angle also is restricted by the equipment size and configuration. Therefore, residues were viewed over a range of angles from 15° to 90°. The minimum angle resulted from a combination of comfortable viewing angle coupled with viewing distance. Intermediate viewing angles of 30° and 45° were evaluated in addition to perpendicular (90° to the observer) viewing.

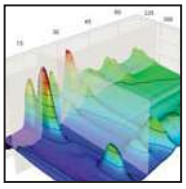
To minimize the effect of observer subjectivity, four subjects viewed all of the samples independently. Sample concentration levels were spotted above and below the previously determined VRL to allow for increased distances and higher intensity light respectively. Therefore, the targeted spotting levels for the formulations were at the swab limit concentration of the API, which is typically 4 µg/cm^2, the previously determined VRL, at the VRL +25% and at the VRL -25%.[10]

Residue appearance varied from white, crystalline to gray. The standard preparation for residue spots involved pipetting 100µl of sample solution or suspension onto the material coupon. This volume of methanol consistently supplied a circular residue spot of about 5 cm in diameter, which was approximately the 25 cm^2 area that was swabbed. As the sample concentrations decreased, the appearance of the residues was less likely to appear as a uniform residue and more likely to appear as a ring. The non-uniform or ring appearance of the residues at the VRL would be observed on equipment after cleaning. As residue levels increase, the VRL would fail a piece of equipment long before it became uniformly coated with residue. A uniformly visible residue would be so far above the VRL, it would indicate a completely ineffective cleaning procedure.

Continued on page 26.

The only complete solution for Process Analytical Technology.

Enable Real-Time Release Through Quality by Design



ABB's Industrial IT for PAT is a globally-supported, end-to-end solution for PAT (Process Analytical Technology) implementation. This system takes full advantage of the FDA's PAT guidance. It supports Quality by Design (QbD) as well as real-time product release initiatives. In addition, it allows online process verification and continuous process improvement. From analyzers and automation to services and support, only ABB stands ready to implement a total PAT solution to keep your plant running smoothly – today!

For more information, visit us at www.abb.com/lifesciences, www.abb.com/analytical or email pharmaceutical.info@us.abb.com.

Power and productivity for a better world™

ABB

Parameter Limitations

As expected, the overall ability to visually detect formulation residue decreased with increased viewing distance[10] - *Figure 1*. At 400 lux and at the minimum viewing angle, observers were able to detect residue at the swab limit concentration, as well as the VRL for all tested formulations from 5 feet. Several of the formulation VRLs were not detected from 10 feet. From 15 feet, the observers were not able to see the majority of the VRLs and were not able to detect any of the VRLs consistently from 20 feet. With regard to the ARLs, the observers saw the majority of the formulation residues under these viewing conditions from 10 and 15 feet[10] - *Figure 2*. From 20 feet, the observers saw less than half of the formulation ARLs.

The ability to detect visible residue also diminished with decreased ambient light[10] - *Figure 3*. With ambient light down to 200 lux, VRLs were consistently detected from 15 feet and a 45° viewing angle. With ambient light at 100 lux, some VRLs were not detected at 15 feet and 45°. However, VRLs were consistently detected from 10 feet at 100 lux.

The ambient light source controlled the light intensity at the lower end of the range. The portable light source controlled the light intensity at the upper end of the range. The observer moved and adjusted the orientation of the portable light source to optimize individual viewing conditions within the constraints encountered in different manufacturing equipment; therefore, the maximum intensity of the portable light source decreased with distance. In general, the use of the spotlight did not increase the observer's ability to detect formulation residue - *Figure 4*.

The viewing angle of the observer to the residue was a critical parameter in the ability to detect the formulation residue. Under ambient light and at the minimum angle, about 15° - *Figure 1*, the observers did not detect the majority of the VRLs at 15 feet and only detected a few at 20 feet. When the viewing angle was increased to 30°, the observers detected more residue spots at both 15 and 20 feet, but not enough to make a significant difference compared to the 15° data. As the viewing angle was increased to 45° and 90°, the observers detected almost all of the VRLs at 15 feet and detected the majority of the VRLs at 20 feet. The observers detected essentially all of the ARLs at 20 feet at viewing angles greater than 30° - *Figure 2*. When the position of the observer was varied with respect to the stainless steel background, observers detected all VRLs from 10 feet at a 45° coupon angle down to 100 lux.

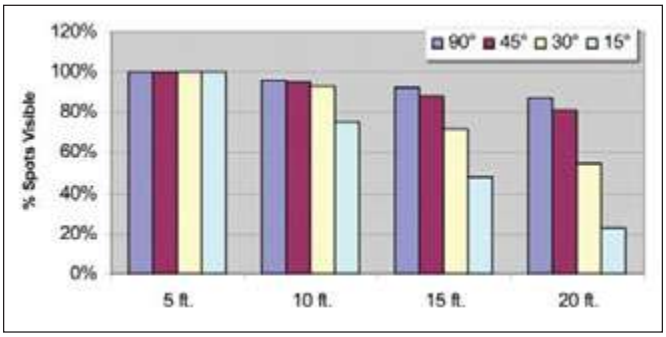


Figure 1. VRL detection versus distance and viewing angle at 400 lux.

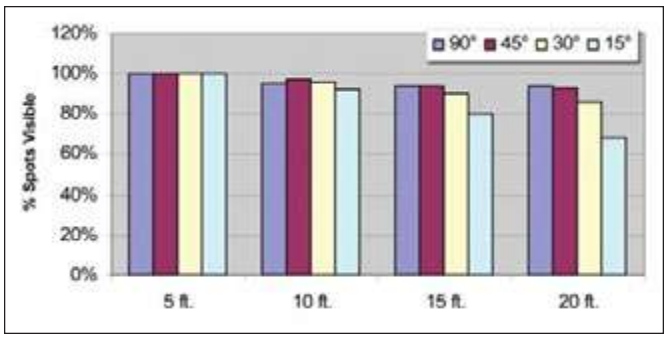


Figure 2. ARL detection versus distance and viewing angle at 400 lux.

Training

Observer variability was a factor in determining the VRL[9] for API and formulation residues. The pool of observers were recruited based on job function, i.e., those performing VRLs, those cleaning the equipment, and those inspecting the equipment. A level of visual acuity is necessary for the various job functions. No additional eye test was required for observers in order to mimic real conditions. The data showed that the observer's ability to see the residues was not a limiting factor to VRL determinations. Each viewing parameter examined had an effect on the observer's ability to detect the formulation residues. Observer detection was dependent on the formulation residue level, observer viewing distance, light intensity, and viewing angle. Certain observers had trouble detecting several of the formulation residues. Observer variability increased with greater viewing distance and became a factor beyond 10 feet. This same trend was seen with the observer angle factor. At the minimum angle of 15° and at 30°, observer variability was comparable to the other parameters. However, at a viewing angle greater than 30°, the ability to detect residue increased significantly and observer variability decreased accordingly - *Figures 1 and 2*. Observer residue detection was comparable using the portable light source and ambient light at 400 lux (Figure 4) and was not a significant factor at decreasing light intensity levels until 100 lux, where detection of VRLs was problematic - *Figure 3*.

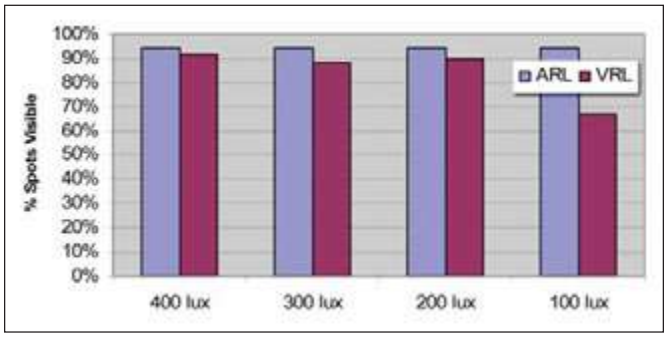


Figure 3. ARL and VRL detection versus decreasing light intensity at 15 ft. and 15°.

Continued on page 28.

A Single Resource...

for TOTAL Cleanroom Confidence.

Planning & executing the right cleanroom solution for your critical process.

AES is your single resource to deliver fast track solutions for Pharma & BIO applications, such as:

- **API Clean Containment**
- **Fill/Finish Processes**
- **Blow/Fill/Seal Facilities**
- **EU/Grade A Laminar Flow Upgrades**
- **Low cost ISO 8/CNC Macro Environments**
- **Cell Manufacturing Facilities**

With the AES Pharma Wall System, combined with our expert knowledge of HVAC and process integration, let us show you how the AES "single resource" team can deliver maximum value to your cleanroom investment.

Call Grant Merrill at 888-237-2532 (ext. 139) to arrange your free consultation today.

VISIT AES AT

Interphex Puerto Rico
Booth 507
Jan. 29 & 30, 2009

Interphex New York
Booth 2928
Mar. 17, 18 & 19, 2009

aes
Clean Technology, Inc.

1-888-AES-CLEAN ext. 139
237-2532

aesclean.com

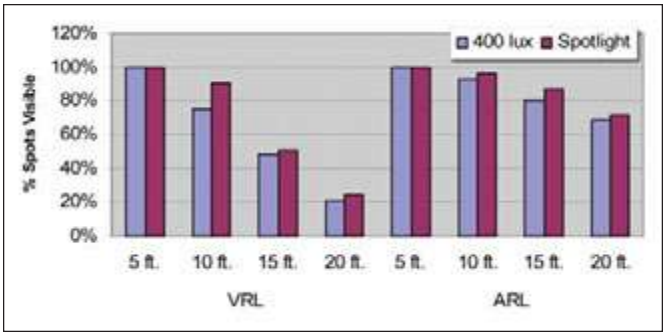


Figure 4. ARL and VRL detection at 400 lux and maximum light intensity at 15 ft. and 15°.

The parameters which influence the ability to detect visible residues were determined and viewing of residues can be controlled. Under defined viewing conditions, a trained observer will be able to visually detect formulation VRLs. The observer should be within 10 feet of the equipment surface. This minimizes the influence of the light intensity or viewing angle. Secondly, the observer should view the surface from multiple angles greater than 30°. This minimizes the possibility of the residue blending in with the background. Finally, the ambient light level should be at least 200 lux. Otherwise a portable light source can be utilized.

VRL Ruggedness

Initial vs. Later VRL Determination

Of the original 59 VRLs established,[9] the average VRL was 1.6µg/cm². Three of the four observers agreed on most residue levels, but one observer differed, which resulted in slightly higher VRLs. Since observer agreement was a condition for the VRL determinations, the individual VRL data points were unaffected by the observer variability. Of the original set of VRLs, 78% were less than 2µg/cm², but 14% were greater than 4µg/cm² - *Table A and Figure 5*. Additional VRL determinations increased the experience level, widened the observer pool, and refined the experimental technique. Instead of a small, dedicated group of observers, the individuals working on the development compound established the VRLs. The observer pool is now between 20 to 30 individuals. However, the most significant difference in the subsequent VRL determinations was the standardization of the residue spot preparations using lower spotted residue levels - *Table B*, which resulted in lower Visible Residue Limits. Interestingly, the variability among the observers decreased even as the observer pool increased. The greater observer consistency was a result of several factors: the initiation of a VRL training program for observers and equipment cleaners and inspectors; the overall increased experience level of the observers and the consistent residue spot preparation technique. Of the additional VRLs established, the average VRL dropped to 0.9 µg/cm² and 89% of the determinations were less than 2µg/cm², 96% of the total were less than 3µg/cm², and only 2% were greater than 4µg/cm² - *Table A*. A t-test comparison of the original and additional VRL data in Figure 5 resulted in a t-stat of 2.45, which is greater than the t-critical value of 1.96 for a two tail comparison with a 95% confidence limit and showed that the data distributions were not equivalent. The additional VRL data with its lower average, were statistically

	Original VRL Data		Subsequent VRL Data	
VRL (µg/cm²)	**Number of Compounds**	**%Total**	**Number of Compounds**	**%Total**
< 1	33	56%	148	76%
1 – 2	13	22%	25	13%
2 – 3	3	5%	14	7%
3 – 4	2	3%	4	2%
> 4	8	14%	3	2%
Total	**59**	**100%**	**194**	**100%**

Table A. Comparison of VRL data.

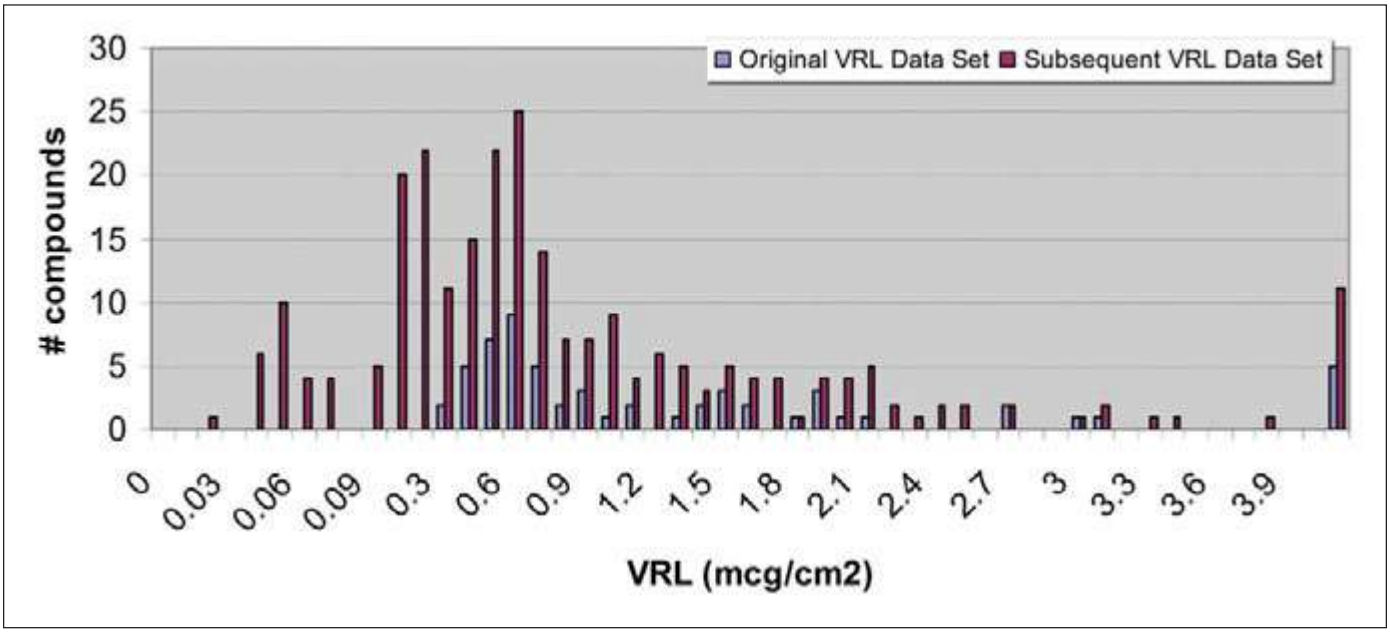


Figure 5. VRL distribution.

Continued on page 30.

Stop wishing. Start saving. The S3℠ System has arrived!

Introducing the S3 System: a revolutionary way to purify water. At Siemens, your wish is our command. Our S3 System significantly lowers your energy and operating costs while lengthening the life of pumps, membranes and other components. Contact your Siemens representative today to learn how the innovative S3 System technology can help make your wishes to reduce operating costs, and to become a "greener" organization, come true.

For more information, call 800.875.7873 ext. 5000 or visit
www.siemens.com/s3

Water Technologies

SIEMENS

Spotting Solution Prep	Residue Spotted	Target Concentration (20 cm^2)
Soln A – 20 mg into 25ml	80 μg	4 $\mu g/cm^2$
Soln B – 5 ml of A into 10 ml	40 μg	2 $\mu g/cm^2$
Soln C – 5 ml of B into 10 ml	20 μg	1 $\mu g/cm^2$
Soln D – 5 ml of C into 10 ml	10 μg	0.5 $\mu g/cm^2$
Soln E – 5 ml of D into 10 ml	5 μg	0.25 $\mu g/cm^2$
Soln F – 1 ml of D into 10 ml	1 μg	0.05 $\mu g/cm^2$
Solvent	0 μg	0 $\mu g/cm^2$

Table B. Residue target concentrations.

VRL ($\mu g/cm^2$)	APIs	Formulations	Excipients	Detergents	Total (%Total)
< 1	76	51	46	8	181 (68%)
1 – 2	18	9	8	3	38 (17%)
2 – 3	10	2	4	1	17 (7%)
3 – 4	3	2	1	0	6 (3%)
> 4	6	0	5	0	11 (5%)
Total	**113**	**64**	**64**	**12**	**253 (100%)**

Table C. Current VRL data.

different when compared to the original VRL data, which confirmed the effects of experience and technique refinement. The overall average VRL is now below 1.1µg/cm^2 for the 253 VRLs determined to date - *Table C* since 63% of the VRLs determined are "less than" the lowest level tested.

API vs. Excipient vs. Formulation Determinations

An analysis was conducted of the VRL data broken down into API, excipients, and formulation categories to determine any VRL correlation between a formulation and its components. Earlier work[9] compared the VRL of 12 formulations against the VRLs of the formulation components. Logically, the VRL of the formulation would be the same as the lowest component VRL. That was the case in seven of the 12 comparisons. However, in three of the cases, the formulation VRL was higher and in the other two, it was lower than the component VRLs.

The more important comparison was between the VRL of the formulation and its API. In the pilot plant, it is not practical to perform a VRL on every development formulation. The formulation compositions continually evolve up to the final market formulation selection. In the VRL comparison of formulations against components,[9] nine of the 12 formulation VRLs were lower than the VRL of the respective API. In one case, they were equal and in the remaining two, the formulation VRL was higher. The data concluded that the VRL of the API is not a good indicator for the VRL of a formulation.

However, the data was generated during the original VRL work, where the residue concentrations and observer variability were higher. The subsequent VRL work generated additional data with increased experience and refined technique. The data gap narrowed between the formulations and APIs. The current average VRL of 64 formulations is 0.7µg/cm^2 and of 113 API determinations is 1.0 µg/cm^2. The average VRL of the 64 excipients tested to date is 1.6 µg/cm^2. The VRL data showed significant overlap among formulations, APIs, and excipients. A t-test comparison of the API and formulation VRL data in Table C and Figure 6 showed that the data distributions were equivalent. The formulation VRL data, despite its lower average value, was not statistically different when compared to the API VRL data. The expanded data set analysis concluded that the VRL of the API was a good indicator for the VRL of a formulation. One can determine the VRL of a development API and safely employ that number as the VRL for the development formulation(s).

Multi-Site Study

The VRL data from the three sites are shown in Table D. Data from the UK site were generally lower than from the other sites. Data from the US site were slightly higher, which correlated to smaller spot sizes and resulting higher spot concentrations.[14] The observers in the UK and US typically were able to detect the lowest or next to lowest residue level. The data from the Canadian site showed three VRLs which were higher than the other sites. Observer variability at Montreal also was greater. Of the three higher levels, one was comparable to the established VRL, while the other two were higher than the established VRL. All three were still well below the adulteration limit of 4µg/cm^2. A review of the observer data showed that in all cases the higher levels were based on one observer not detecting the residue. Otherwise the data more closely agreed with the other sites.

The variability of the multi-site data was the result of several factors. The sample solution concentrations, spot sizes, and the resulting residue concentrations influenced the VRL determination. The UK site's lowest residue level was lower than the other sites, which explained their overall lower VRL levels. The observer variability at the Canadian site was similar to the early US site data. A single observer skewed the results compared to the other observers and other sites.

Two grades of stainless steel finish were evaluated. The majority of process equipment is mill (matte) finish, but the use of mirror (electropolish) finish equipment has increased. There were no consistent differences between the VRL results from the mill and mirror stainless steel finishes. The

Compound	Established VRL ($\mu g/cm^2$)	U.K. VRL ($\mu g/cm^2$)		U.S. VRL ($\mu g/cm^2$)		Canadian VRL($\mu g/cm^2$)	
		Mill	Mirror	Mill	Mirror	Mill	Mirror
A	0.67	< 0.29	< 0.25	< 1.06	< 0.83	2.00	< 0.22
B	0.485	< 0.33	< 0.28	< 0.52	< 0.40	0.64	1.33
C	< 0.36	< 0.26	< 0.53	< 1.12	< 1.12	0.61	< 0.23
D	2.05	< 0.49	< 0.52	< 0.93	< 0.56	2.29	< 0.23
E	< 0.61	< 0.23	< 0.25	< 0.42	< 0.64	2.00	0.47

Table D. Multi-Site VRL data (mill finish and mirror finish stainless steel).

VRL Application	Pilot Plant/Manufacturing	Process Risk	Risk Mitigation
New Compound Introduction	Pilot Plant	**Low** New worst-case	· VRL determination · Redundant inspection · Evaluate API physical properties
New Compound Introduction	Manufacturing	**Low** New worst-case	· Redundant inspection · Evaluate formulation physical properties and cleanability
Routine Use Inspection	Pilot Plant	**None**	· Already in place · Cleaning validation
Routine Use Inspection	Manufacturing	**None**	· Already in place · Cleaning validation
Periodic Assessment	Pilot Plant	**Low** Carryover	· Redundant inspection · Periodic swab confirmation
Periodic Assessment	Manufacturing	**Low** Carryover	· Redundant inspection · Periodic assessments trending performance based on visual inspections.
Technology Transfer	Pilot Plant	**Low**	
New Equipment Introduction	Pilot Plant	**Low** Cleaning procedure doesn't work	· Redundant inspection · Evaluate versus current equipment
Campaign Length Extension	Manufacturing	**Low to None**	
Cleaning Procedure Optimization	Pilot Plant	**None**	· Surface sampling after optimization
Cleaning Procedure Optimization	Manufacturing	**None**	· Surface sampling and validation after optimization
Reduced Cleaning Documentation (Manual Cleaning, Equipment accessible to visual inspection)	Manufacturing	**Low to None**	· Data to demonstrate VRL < ARL · All cleaning parameters demonstrated during validation

Table E. VRL application and risk assessment.

finish of the stainless steel had no impact on the VRL determinations.

It was concluded from the study that VRL determination was comparable at the three sites and the experimental

Continued on page 32.

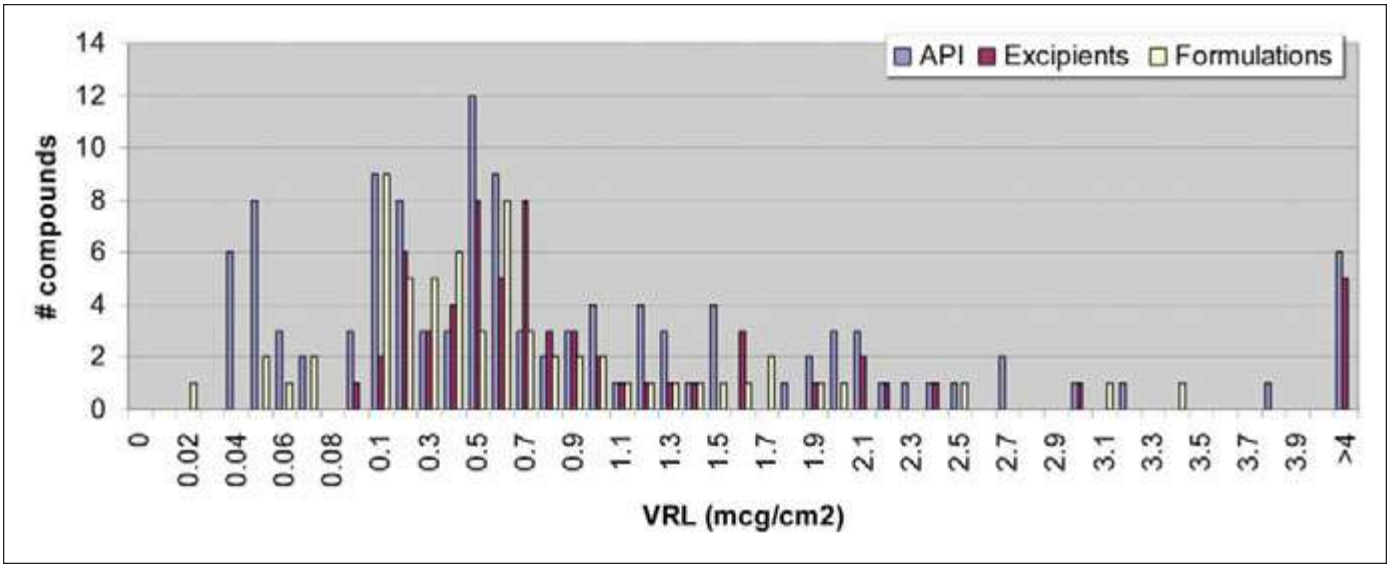


Figure 6. VRL distribution.

variability from sample preparation and observer subjectivity posed no risk for a potential cleaning failure since all VRL values were well below the ARL. The study also pointed out the value of VRL training program and the experience gained through ongoing visual equipment inspections.

Residue Appearance

The standard preparation for residue spots involved pipetting 100µl of sample solution or suspension onto the material coupon. This volume of methanol consistently supplied a circular residue spot of about 5 cm in diameter, which was approximately the 25 cm^2 area that was swabbed. As the sample concentrations decreased, the appearance of the residues changed from a uniform residue to that of a ring - *Figures 7 and 8*.

To determine the effect of spotting volume, 60µl of the lowest spotted solution was pipetted along with 0, 20, 40, 60, 80, and 100 µl of methanol. The lowest concentration was used since the appearance of the residue near the VRL was the primary area of interest. The appearance of the different volumes had little effect on the appearance of the residue around the VRL. All of the residues were similar, but as expected the rings became larger with the increased volume - *Figure 9*. Eventually, larger volumes of spotting solvent would make the ring too dilute to detect, but the area of the ring at that point would be significantly larger than the swab area of 25 cm^2.

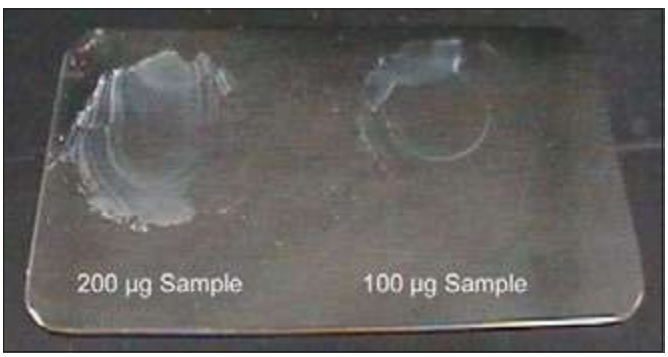


Figure 7. Effect of concentration on residue appearance.

It can be concluded that the appearance of residues near the VRL concentration are expected to take on the appearance of a ring. If the residue has a uniform appearance, it is most likely well above the VRL limit.

Applications

Uses of VRLs by a Pilot Plant Facility

The use of VRLs has previously been described[9,11] for the introduction of new compounds into a pilot plant. Before a new compound is manufactured in the pilot plant, a VRL is established for the API. After the initial batch is manufactured, the equipment is cleaned and visual inspection using the VRL confirms the current cleaning procedure is sufficient and that the new compound is not a new worst-case requiring further validation. This application along with its risk mitigation is shown in Table E.

VRLs also are used for periodic assessment of cleaning in the pilot plant. Monthly independent visual inspections using VRLs are conducted on several pieces of equipment to assure that routine cleaning removes all product residues. Over the course of the year, these independent periodic inspections check all of the different types of equipment in the pilot plant to generate a comprehensive review of ongoing cleaning effectiveness in the pilot plant.

Other uses of VRL in the pilot plant include technology transfer either to a contract or a manufacturing facility. Since cleaning procedures between facilities are different, VRLs would be a quick, simple verification of cleaning in place of analytical method transfer and testing. VRLs also can be used for the introduction of new equipment into the facility. VRLs would be an efficient way to get equipment on line and ensure baseline cleanliness, while demonstrating equivalency with respect to the cleaning efficacy of a previously validated procedure.

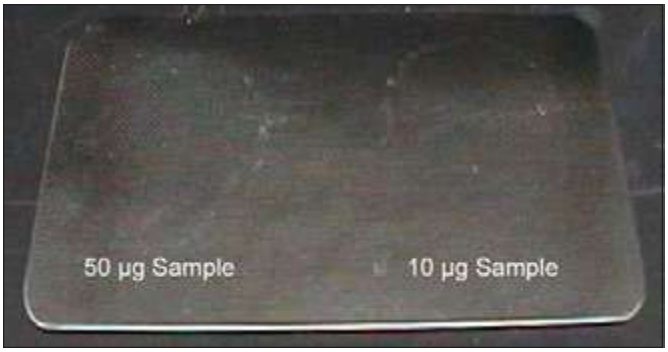


Figure 8. Effect of concentration on residue appearance.

The optimization of new cleaning procedures during development is another application for VRLs. Cleaning cycle times could be challenged with VRL determination as the acceptance criteria. A more immediate benefit would be realized with manual cleaning procedures. Personnel who clean the equipment could effectively determine optimal scrub times and rinse volumes with a visual limit.

Uses of VRLs in a Manufacturing Facility

Several opportunities to apply VRL as a surrogate to surface sampling have been identified in manufacturing facilities using Good Manufacturing Practices (GMPs). Process controls and procedures also have been identified to mitigate the risks when applying VRL in a GMP facility. Given that VRL determinations for drug product formulations have been established[9,10] and the relative accessibility to visual inspections with this equipment, the scope of these applications would be primarily applicable to pharmaceutical manufacturing and primary packaging operations.

As with pilot plant facilities, VRL data may be used to develop new or optimize existing cleaning procedures. The extent of routine documentation and cleaning records could be streamlined in a GMP facility. Once optimal scrub times and rinse volumes have been validated and incorporated into the cleaning procedure, visual cleanliness may be the only critical cleaning parameter that would require documentation on a routine basis. With VRL data, a check by a second person for visual cleanliness confirms performance and ensures that the level of residuals is below the acceptable residue level. This procedure may obviate the need to record actual cleaning parameter data (i.e., scrub times and rinse volumes) on a routine basis and reduce the volume of GMP documentation that must be maintained for marketed drug products.

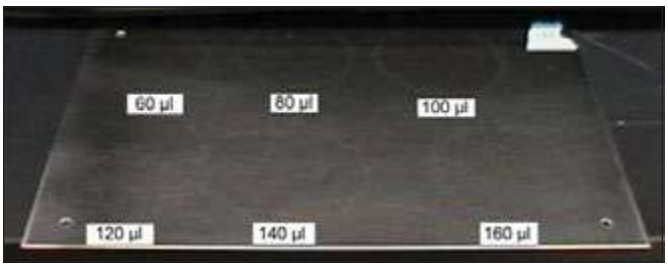


Figure 9. Effect of volume on residue appearance – 6 µg sample.

VRL data and visual inspection may be applied to support the introduction of new products into existing validated product matrices. The use of product matrices or bracketing product residues to validate a "worst case" for multi-product equipment modules is a common practice in industry and supported by regulatory guidance.[2,15-17] If not a new worst-case, the VRL of the new compound can be compared to the validated ARL. If the new compound is less than the ARL, visual inspection alone should be satisfactory for revalidation of the cleaning procedure for a new product.

The interval of use (manufacturing campaign) and the interval between end of use and cleaning are process parameters that must be validated. For stable products manufactured in freely draining equipment, there should be low-to-no process risks with respect to extending a validated campaign length based on visual inspection. Routine inspections for visual cleanliness would mitigate any potential process risks with carryover of process residuals and confirm cleaning performance. The risks for bioburden proliferation are low due to the absence of water and moisture. This same rationale could be applied to extending validated times for the interval between the end of use and equipment cleaning.

Once a cleaning process is validated in a GMP manufacturing environment, the process should be monitored periodically to ensure consistent and robust performance. Independent visual inspections should be incorporated into the peri-

Concludes on page 34.

odic assessment program to confirm that the cleaning processes remain in a state of control. A second person should check for visual cleanliness and the frequency of recleaning is an appropriate metric for assessing cleaning performance. This additional control helps to ensure robustness of the validated cleaning procedure. With an appropriate VRL program, visual inspection may be used rather than surface or reinstate testing to demonstrate continued consistent cleaning performance.

Conclusion

Visible Residue Limits (VRLs) have been evaluated for pilot plants and manufacturing facilities from a risk-assessment perspective. The VRL data, particularly when compared to the health-based cleaning limit for most compounds, makes VRL use a low risk approach to cleaning verification and validation. The ruggedness of VRL viewing conditions has been tested and optimal viewing conditions defined. The current studies established the ruggedness of VRL determination among multiple observers at different sites, showed the relationship between VRLs of formulations and individual components, and assessed the effects of residue appearance on VRL preparation parameters. The studies also highlighted the value of a VRL training program for all personnel involved in the program. Opportunities for VRL implementation have been identified along with the acceptable mitigation of the associated risks.

References

1. Mendenhall, D.W., "Cleaning Validation," Drug Development and Industrial Pharmacy, Vol. 15, No. 13, 1989, pp. 2105-2114.
2. FDA, "Guide to Inspection of Validation of Cleaning Processes," (Division of Field Investigations, Office of Regional Operations, Office of Regulatory Affairs, July 1993).
3. LeBlanc, D.A., " 'Visually Clean' as a Sole Acceptance Criteria for Cleaning Validation Protocols," PDA J .Pharm. Sci. and Technol., Vol. 56, No. 1, 2002, pp. 31-36.
4. Jenkins, K.M. and Vanderwielen, A.J., "Cleaning Validation: An Overall Perspective," Pharm. Technol., Vol. 18, No. 4, 1994, pp.60-73.
5. Forsyth, R.J. and Haynes, D., "Cleaning Validation in a Pharmaceutical Research Facility," Pharm. Technol., Vol. 22, No. 9, 1998, pp.104-112.
6. LeBlanc, D.A., Danforth, D.D., and Smith, J.M., "Cleaning Technology for Pharmaceutical Manufacturing," Pharm. Technol., Vol. 17, No. 10, 1993, pp. 118-124.
7. Forsyth, R.J., Leblanc, A., Voaden, M., "A Single Adulteration Limit for Cleaning Validation in a Pharmaceutical Pilot Plant Environment", Pharm. Technol., Vol. 31, No. 1 2007, pp. 74-83.
8. Fourman, G.L. and Mullen, M.V., "Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations," Pharm. Technol., Vol. 17, No. 4, 1993, pp. 54-60.
9. Forsyth, R.J. and Van Nostrand, V., "Visible Residue Limit for Cleaning Validation and its Potential Application in a Pharmaceutical Research Facility," Pharm. Technol., Vol. 28 No. 10, 2004, pp. 58-72.
10. Forsyth, R.J. and Van Nostrand, V., "Application of Visible Residue Limit for Cleaning Validation in a Pharmaceutical Manufacturing Facility," Pharm. Technol., Vol. 29, No. 10, 2005, pp. 152-161.
11. Forsyth, R.J. and Van Nostrand, V., "The Use of Visible Residue Limit for Introduction of New Compounds in a Pharmaceutical Research Facility," Pharm. Technol., Vol. 29, No. 4, 2005, pp. 134-140.
12. Forsyth, R.J., Hartman, J.L., and Van Nostrand, V., "Risk-Management Assessment of Visible Residue Limits in Cleaning Validation," Pharm. Technol., Vol. 31. No. 4, 2007, pp. 134-140.
13. Forsyth, R.J., Lukievics, T., Roberts, J., and Van Nostrand, V., "Correlation of Visible Residue Limits with Swab Results for Cleaning Validation," Pharm. Technol., Vol.30, No. 11, 2006, pp. 90-100.
14. Forsyth, R.J., et al, Internal Report: Multi-Site Study for Visible Residue Limit Determination in the Solid Dosage Pilot Plants, 22 January 2008.
15. EudraLex, Annex 15, "Qualification and Validation."
16. Pharmaceutical Inspection Co-operation Scheme (PIC/S), "Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-sterile Process Validation, Cleaning Validation.
17. Health Canada , Health Products and Food Branch Inspectorate, "Cleaning Validation Guidelines."

About the Author

Richard Forsyth is an Associate Director with GMP Quality at Merck & Co., Inc. He is responsible for internal and external facility audits, as well as document audits for regulatory submissions. He has worked in Quality for three years and prior to that worked as an analytical chemist in Pharmaceutical R&D for 23 years. He has been involved with cleaning validation for more than 15 years. Forsyth has a broad range of GMP/GLP analytical experience, including methods development and validation as well as formulation development and project management. He is an adjunct Professor in the QA/RA graduate program at Temple University. Academic training includes an MS in chemistry and an MBA in management, both from St. Joseph's University in Philadelphia, Pennsylvania, USA. He can be contacted by telephone: +1-215-652-7462 or by email: richard_forsyth@merck.com.

Merck & Co., Inc, Worldwide GMP Quality, WP53C-307, West Point, Pennsylvania, 19486, USA.

In this interview, senior staff members from China's State Food and Drug Administration share the latest developments and achievements of China's activities in drug manufacturing and supervision of drug safety, and ideas for future potential cooperation with ISPE and other international organizations in the industry.

PHARMACEUTICAL ENGINEERING Interviews

Senior Staff Members from China's State Food and Drug Administration (SFDA)

by Robert P. Best, Robert W. Tribe, Paul N. D'Eramo, and Cheryl Siow

Editor's Note: In light of the burgeoning pharmaceutical industry in Asia, ISPE's involvement with activities in this region is growing rapidly, especially in China. Last year, ISPE made several monumental strides to build a presence in a country that continues to increase its role on the world stage.

In 2008, ISPE opened an office in Shanghai; recruited close to 30 local volunteers who are forming ISPE's first China Affiliate; started ISPE's first Student Chapter with more than 100 members at Sichuan University; and joined forces with the China Center for Pharmaceutical International Exchange (CCPIE) to bring education programs to Chinese pharmaceutical professionals at the ISPE China Conference in November in Beijing.

Moving into 2009, there will be more activity to come. Pharmaceutical companies will increasingly rely on China for integrated research, development, and innovative manufacturing solutions. The Chinese pharmaceutical government and industry are aware that to move beyond imitation toward innovation, they must have an educated workforce trained in the latest technologies and informed about the latest global regulations.

As a neutral organization that promotes worldwide collaboration to improve the industry on a scientific and technical basis, ISPE met with senior staff members from China's State Food and Drug Administration (SFDA) in November in Beijing to share ideas and information.

In addition, Robert P. Best, President and CEO, ISPE, Robert W. Tribe, ISPE Asia-Pacific Regulatory Affairs Advisor, Paul N. D'Eramo, Executive Director, Johnson & Johnson, Global Quality, ISPE Past Chairman, and Cheryl Siow, Manager, ISPE China Office, conducted an interview with the following SFDA officials on behalf of *Pharmaceutical Engineering*:

- JiangYing Yan, Spokeswoman of SFDA, Deputy Director-General, Department of Policy and Regulations, SFDA
- WenZuo Chang, Counsel, Department of International Cooperation, SFDA
- JianHua Ding, Director, Division of Pharmaceuticals, Department of Drug Registration
- Ai Liu, Consultant of Liaison Division, Department of International Cooperation, SFDA
- QingWu Guo, Deputy Director, Division of Drug Manufacturing Supervision, Department of Drug Safety and Inspection, SFDA
- Zhongzhi Qian, Professor, Director, Division of TCMs Standard, Chinese Pharmacopoeia Commission
- Lili Cao, Director, Division of External Cooperation, CCPIE, SFDA

More comprehensive information on the current state of China's pharmaceutical industry is available in the Country Profile on China, a Supplement included with this issue of *Pharmaceutical Engineering*.

• • •

JiangYing Yan We know that *Pharmaceutical Engineering* is a world-renowned publication of ISPE. We hope to share with the world the latest developments and achievements of China's activities in drug manufacturing and supervision of drug safety and the future potential cooperation.

Continued on page 38.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2009,
Vol. 29 No. 1

In commissioning, validation and compliance, teamwork and timing are everything.

COMMISSIONING AGENTS. We're in position, skillfully negotiating every turn to help you get to your project's finish line faster and more efficiently. Our teams undergo a rigorous program of structured training, qualification, and continuous professional development. You'll find we aren't selling individual resumes, we're selling a high performance team.

For every project, teamwork and timing are everything.

- **Commissioning planning and field execution**
- **Validation planning, protocol development and execution**
- **Process validation, cleaning, sterilization and computer validation**
- **Process improvement services: Process Analytical Technology (PAT), technology transfer and process studies**
- **Technical services including design reviews, SOP development, maintenance programs and training**
- **cGMP compliance audits and regulatory reviews, compliance improvement projects, comparability protocols and other submission assistance**

CAI Commissioning Agents, Inc.

WWW.COMMISSIONINGAGENTS.COM

Achieve world class manufacturing.

Call Robert E. Chew, P.E., Vice President
Robert.Chew@CAgents.com
+1.317.710.1530

"ICH played a very important role in China's regulatory system. We adopted many guidelines from ICH in drafting our local technical guidelines."

Q What is the status of the revised China GMPs?

QingWu Guo I would like to briefly introduce the process of the revision work on the China GMPs which will help you understand our work. We started revising GMP Revision 98 four years ago. We conducted a study on all the available GMP guidelines in the world for two years. The study covers the GMPs of the Australian Therapeutic Goods Administration (TGA), the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S); the European Medicines Agency (EMEA); the World Health Organization (WHO); the US Food and Drug Administration (FDA); and the Japanese Ministry of Health, Labour and Welfare (MHLW). We began to revise the current GMPs after the study and comparison. The first draft of the GMP has been completed and we will post it on the SFDA Web site to solicit opinions at the end of this year or early next year. If you have a chance to look at the draft, you will find the new revision of the GMPs is quite similar to what the EMEA and the WHO have, but some of the format has been tailor-made for China. We welcome ISPE's suggestions and opinions on the draft.

I would like to address that we included a detailed appendix on Traditional Chinese Medicines (TCMs). It might be different from other countries since TCMs have many kinds of formulations, including sterile and non-sterile. According to the specialties of TCMs, we set up detailed regulations, especially for the process of the pretreatment, which is not required in other countries. China has Good Agricultural Practices (GAP) on TCM manufacturing and we require a GAP inspection on the source of TCM before the GMP inspection for some TCM drug products.

Q You mentioned that the draft will be available on the Web site at the end of this year. Will there be a transition period for the local manufacturers and individuals overseas to make comments?

From left to right: Cheryl Siow, Paul N. D'Eramo, Robert W. Tribe, Robert P. Best, JiangYing Yan, WenZuo Chang, QingWu Guo, Prof. Zhongzhi Qian, Ai Liu, and Lili Cao.

QingWu Guo Definitely. The period will be at least three months or more to solicit opinions and suggestions twice.

Q How is the SFDA cooperating with ICH?

JianHua Ding ICH played a very important role in China's regulatory system. We adopted many guidelines from ICH in drafting our local technical guidelines. I believe ICH is not only very important for our regulatory system, but also for the industry. We send Chinese delegates to attend many ICH conferences to learn and study their progress. We also learn ICH guidelines through many ways. We organize several workshops each year with relevant ICH authorities, such as the ICH Global Cooperation Group (GCG). This helps us to study and understand ICH technical guidelines. In addition, we have several experts who have been involved in the drafting of ICH guidelines, such as ICH Q10 and Gene Therapy guidelines.

I am involved in ICH Q10. The SFDA also sends people on behalf of the Life Science Innovation Forum (LSIF) to the ICH GCG. In February, ICH GCG invited six country members, including China, to attend the ICH GCG meeting in Portland.

Q Will the SFDA plan to apply for PIC/S?

QingWu Guo We know that PIC/S is recognized as an excellent GMP inspection cooperation organization. There is mutual learning, information, and resource sharing among the members. We feel that there is mutual recognition in PIC/S. Therefore, we think we could benefit a lot by mutual sharing in PIC/S.

As PIC/S is a country membership, we believe participation of China in PIC/S will promote GMP development.

Continued on page 40.

UNLOCKING VALIDATION SOLUTIONS

As a multinational contract validation service provider,
Validation Technologies Inc. is committed to providing the highest quality validation services and personalized support.

- Quality and Regulatory Services
- Project Management
- Validation Master Plans
- Computer Validation
- Cleaning Validation
- Process Validation
- Commissioning & Technical Services
- Clean Room Certification
- Third Party Certification Process
- Temperature Mapping
- Qualification of Pharmaceutical, Neutriceutical, Medical Device, and Biotechnology Facilities to meet EU, FDA, and any other International Regulations

Validation Technologies, Inc. is pleased to announce the establishment of a new representative office in Shenzhen, China. This presence in the global market further advances VTI as a leading validation service and cGMP consulting firm in the biotechnology industry.

Additional offices in San Diego, Los Angeles, San Francisco, Scottsdale, Boston, Philadelphia, Toronto, and Puerto Rico. We look forward to welcoming you to our new office in China!

Validation Technologies, Inc.
11590 W. Bernardo Court, Suite 245
San Diego, CA 92127
Phone (800) 930-9222
Fax (858) 673-3677
validation@validation.org

Validation Technologies, Inc. (Shenzhen)
19 Gaoxinzhongyi Road, Nanshan District,
Shenzhen, P.R. China
Phone: 86-755-86142174
vti.china@validation.org

For more information visit
www.validation.org

"...China has 4,682 companies which are API and drug manufacturers. Among them, 1,900 companies are TCMs manufacturers. A lot of companies produce Chinese medicines, chemical drug, and biological products at the same time."

However, being a nation with a 1.3 billion population and more than 4,600 manufacturers, we are evaluating the participation in PIC/S. You will hear our voice on this in the near future.

WenZuo Chang I would like to introduce you briefly to the international cooperation mechanism and general situation of the SFDA.

The SFDA attaches great importance to and participates diligently in the international exchange and cooperation on drug administration including international activities of drug safety. We actively develop collaborations with international organizations and other national drug regulatory agencies around the world.

In regard to the cooperation with government agencies, we have signed a cooperation agreement or Memorandum of Understanding (MOU) with more than 10 agencies from the US, Canada, France, the UK, EMEA, Italy, Australia, Cuba, Brazil, South Korea, Singapore, Thailand, etc. Therefore, SFDA has preliminarily formed the pattern of intensive cooperation combined with extensive cooperation with its foreign counterparts.

Very importantly in the international cooperation, the SFDA pays close attention to reinforcement of the cooperation on traditional medicines, for China, they are TCMs and ethnic medicines. The SFDA has good cooperation on TCMs and herbal medicines standards with the WHO, Forum of Herbal Medicine Harmonization (FHH), in the Western Asia Pacific Region and a number of countries, such as the US, France, the UK, the Republic of Korea, etc.

In addition, we also have cooperation with governmental international organizations and other international organizations in the drug regulatory sector, especially with the WHO in facilitating the system of national essential medicines, GMP, traditional medicines, the enhancement of vaccine management, and the development of anti-malaria medicines, which has achieved positive results. The cooperation is on the basis of mutual benefits. In the international activities, we also perform the international obligations meticulously, and always refer to the international best practices and experiences in drug administration and practice it under the Chinese context, for instance, in those mentioned by Mr. Ding and Mr. Guo regarding the cooperation with ICH, and considering to participate in activities of PIC/S. The SFDA has learned lots of valuable experiences, shared from the all international activities, which helps in raising the level and capacity of China's drug administration and to be in line with the international practice.

Q Will the SFDA set up a special inspection department for TCM?

QingWu Guo I would like to clarify that China has 4,682 companies which are API and drug manufacturers. Among them, 1,900 companies are TCMs manufacturers. About 40% of the drug manufacturers are TCMs manufacturers. A lot of companies produce Chinese medicines, chemical drug, and biological products at the same time. There are more than 800 manufacturers which produce TCM preparations only. SFDA has a Division responsible for registering TCMs in the Drug Registration Department. Other than this, we do not have other specific departments for regulating TCM; however, we do have specialists responsible for that.

JiangYing Yan Let me add that during the development of Chinese medicine in our country, we need to ensure safety and quality while we reserve the tradition and encourage innovation at the same time. As what has been applied to chemical drugs, the first priority is to ensure the safety and effectiveness.

Q How can ISPE be supportive of the Chinese pharmaceutical industry?

QingWu Guo Based on my understanding of ISPE, your organization has a lot of cooperation with the China Center for Pharmaceuticals International Exchange (CCPIE). I suggest ISPE look into two areas should you wish to have a wider cooperation with China. First is to establish cooperation with the China pharmaceutical industry, such as through exhibitions and forums/conferences, as what ISPE has done during China-Pharm this year. My second suggestion is to cooperate with government agencies, e.g., the SFDA by providing GMP training to inspectors or assistance with on-the-job training in international inspections. For example, we have trained 100 inspectors on international inspections. Perhaps ISPE could support us in this area. Another aspect of cooperation will be providing comments and suggestions after we announce the GMP revision.

We also hope ISPE can recommend to us the latest information on the GMPs. We understand that ISPE has many of the latest guidances, requirements, and standards. We know that ISPE has a great pool of technical experts worldwide on developing practical standards, which I believe will be very useful to help improve the GMP activities in China.

Zhongzhi Qian I would like to introduce the international cooperation development on drug standards. Drug standards have been widely communicated between countries and many cooperation relationships have been established with many countries. We

have developed international cooperation through three channels: First, the WHO, second, the National Drug Regulatory Agency, and third, the international organizations on drug standards.

I would like to focus on the international cooperation situation on TCM standards. We started cooperation with the WHO in 1979 when Mr. Yuan Shicheng, the Secretary-General of the Chinese Pharmacopoeia Commission was nominated as WHO Foreign Expert for the first time. In 2002, China, Japan, Korea, Singapore, Vietnam, Australia, and Hong Kong SAR established the Western Asia Pacific Forum of Herbal Medicine Harmonization (FHH) under WHO's initiative. FHH's goal is to promote the coordination and development of traditional and herbal medicines standards within Western Asia Pacific countries.

On the subject of cooperation with the National Drug Regulatory Agency, there is effective cooperation between the SFDA and the French AFSSAPS. We have had cooperation since 2000. We have 27 Chinese crude drugs recorded in the French list of medicinal plants, of which seven are in the French pharmacopoeia, and five were recommended into the European pharmacopoeia by the French pharmacopeia.

With regard to cooperation with international organizations on drug standards, we have had cooperation on cooperative research and mutual recognition mechanism of TCM standards with the US, European, and British pharmacopoeias. In April 2008, an MOU was signed with the USP for 2008-2010, which is an extension of the MOU for 2005-2007. The MOU covers the drug standards between the two countries. First is the harmonization of the analytical methods, and then the cooperation and coordination on drug standards focusing on TCMs, as well as on chemical and biological products.

JiangYing Yan ISPE has a strong body of technical knowledge and resources, including standards, regulations, technical documents; these will really help our pharmaceutical industry and drug supervision. In the future, we at SFDA, including CCPIE, will further strengthen cooperation with ISPE.

This report presents the results of the FMI/CMAA Ninth Annual Survey of Owners and provides insight into how companies with ongoing capital construction programs manage risks on projects.

Beyond the Bell Curve: A Report on Managing Capital Project Risk

by Jeff Lukowski and Mark Bridgers

Complexity creates risk and drives an increase in both its frequency and impact. In a world that is growing more complex, global, and interconnected in ways poorly understood, but recently revealed during the US financial crisis, a better way to manage construction risk is a necessity. The results of the Ninth Annual Survey of Owners, recently conducted by the Construction Management Association of America (CMAA) and FMI Corporation, will focus on providing a better way to manage construction risk.

Owners, contractors, engineers/architects, and material or equipment suppliers are just a few of the players that are involved and participate in the construction of facilities and infrastructure. While this study is targeted at understanding owners' perspectives, the risk mitigation strategies they choose to employ, and their ramifications are applicable to all players. In this study, these risk mitigation strategies are divided into four categories: Accept and Manage, Accept and Transfer, Recognize and Ignore, and Avoid. Within each category there are numerous potential strategies. The top five strategies for managing risks are: 1. Integrate Risk into the Contract, 2. Use Standardization, 3. Hire Internal Staff, 4. Increase Team Meeting Frequency, and 5. Request Budget Increases.

Four risks exhibited both very high frequency and major impacts to capital construction projects. Governmental regulation, inaccurate budgeting or estimating by the owner, availability of qualified construction firms and worldwide commodity demand. The first is forced upon many owners and requires strategies focused on influencing the development and application of these regulations. The second is self-created in many instances, due to a lack of recognition of the improbable event, what Nassim Nicholas Taleb describes as a Black Swan in his recent book, "The Black Swan." The latter two revolve around market supply and demand issues. The frequency of all four of these risks dictates that they are routinely managed by owners and when possible transferred.[1]

The reader is encouraged to keep the following in mind as he/she considers how to mitigate risk in today's capital construction world.

- Using past history as a guide for understanding future risk is necessary, but not all encompassing – history is less applicable today because complexity is changing the nature of the game.
- The design and construction mind searches for historical order and patterns to better understand the environment; yet random events will happen. The most severe impacts to capital construction programs noted by the survey respondents fall into the Cost Other = Unanticipated Costs category where they related unpredicted, one-time events that devastated the project or program.
- It is much easier to plan, obtain financing, and hire service providers by ignoring the possibility that a Black Swan-type event may take place, but take place it will.
- History takes the sharp edges off unpredicted, one-time events that devastated the project, compelling practitioners to underestimate the probability that a one-time event is not really a one-time event. The destruction of the Wheeling Suspension Bridge in 1849 and subsequent destruction of the Tacoma Narrows Bridge in 1940 is an example.
- Focusing on the well-defined sources of uncertainty is the normal practice in the industry where numerous experts prepare writing and research to identify an all-encom-

Continued on page 44.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2009,
Vol. 29 No. 1

ELETTRACQUA

pure water technologies

SINCE 1966

PHARMACEUTICAL WATER SYSTEMS

DOUBLE PASS REVERSE OSMOSIS HIGH TEMPERATURE SANITIZATION

DESIGN AND CONSTRUCTION OF PURIFIED WATER PACKAGES • DOUBLE PASS REVERSE OSMOSIS • R.O. + ELECTRODEIONIZATION HOT WATER SANITIZABLE • ULTRAFILTRATION • MULTIPLE - EFFECT DISTILLATION UNITS • PURE STEAM GENERATORS • STORAGE AND DISTRIBUTION LOOP • COMPLETE TURN KEY PROJECTS • VALIDATIONS IQ, OQ

www.elettracqua.com

visit us at
ACHEMA 2009
Frankfurt am Main/Germany
11.–15. 5. 2009
hall 4.1 - stand L20/L22

Highest Frequency Risks	Software Highest Impacting Risks*	Favorite Strategies, Tactics and Processes
1. Commodity Demand	1. Estimating Accuracy	1. Integrate Risk into the Contract
2. Energy Prices	2. Government Regulations	2. Use Standardization
3. Skilled Craftsmen	3. Commodity Demand	3. Hire Internal Staff
4. Estimating Accuracy	4. Construction Firms	4. Increase Team Meeting Frequency
5. Construction Service Demand	5. Construction Service Demand	5. Request Budget Increase
* excluding self-selected other responses		

Table A. Top five risks and strategies.

passing list of design and construction risks – we must see the forest *and* trees for success, recognizing that the most devastating risks will originate from the forest, which is harder to see and discuss.

Survey Highlights

The highest-observed frequency and impact risks, along with the favorite strategies, tactics and processes to address them, are detailed in Table A. The highlights of the survey include the following:

- **Throwing Money at the Problem:** 33 percent of the time owners request a budget increase to manage project or program risks.
- **Application of Leverage:** 75 percent of the time owners use some form of program-level purchasing power to transfer or manage project or program risks.
- **Hammer Looking for a Nail:** 25 percent of the time owners use the same strategy, tactic, or process to address both frequency and impact (severity) without recognizing the different challenges of each.
- **Tunneling:** Seven out of 28 survey risks were rated with both low frequency and impact, indicating a focus on a few well-defined sources of risk.
- **Black Swans Do Exist:** With only two exceptions, an "immense" impact was reported by multiple survey respondents in every risk description presented, indicating that every risk has the potential for catastrophe.
- **The Impact of the Highly Improbable:** "Major" and "Immense" impact were most frequently reported in "Cost Other = Unanticipated Risks" category where respondents described unpredicted, one-time events that devastated a project or program 22 percent of the time.
- **Greatest Fear:** Schedule impact was described as the greatest negative outcome to project or programs; nearly twice as many "Major" and "Immense" impacts were described versus the other impact categories of financial (cost) or qualitative (public or internal reputation, quality or safety).
- **Size Matters:** The biggest capital construction programs choose to "Accept and Manage" risk nearly 70 percent of the time (50 percent more than the smallest programs that "Avoid" or "Accept and Transfer" nearly 60 percent of the time).
- **Risk Appetite Matters:** Financial institutions, real-estate developers, and sports authorities have the lowest risk appetite and frequently choose to "Avoid" or "Accept and Transfer" risk, while chemical companies, energy firms, and various types of manufacturers tend to have the highest risk appetite and "Accept and Manage" risks frequently.
- **Consistent Strategy Use:** Owners elect to either "Accept and Manage" or "Accept and Transfer" the 28 risks included in the survey 61 percent and 22 percent of the time, respectively.
- **Avoidance:** 41 percent of the time when inability to effectively plan is perceived as a risk, owners prefer to avoid the project rather than ignore, manage, or transfer the risk.
- **Management:** 38 percent of the time when inability to estimate accurately is perceived as a risk, owners prefer to accept and manage the risk rather than avoid, ignore, or transfer.

Risk Management Focus

The focus of the FMI/CMAA *Ninth Annual Survey of Owners* is on understanding how program- or project-level risks are assessed and managed prior to or during project execution (planning through turnover) and how they impact an owner's overall capital program. Life Science industry participants represented more than ten percent of the total participation. FMI analyzed the frequency of occurrence and severity of impact of specific risks, and more broadly, how owners tend to manage construction risks by electing to use certain strategies, tactics or processes.

FMI/CMAA worked with a team of highly experienced industry professionals to establish a common definition of risk management in the survey. Although the general topic of risk management in the construction industry covers a broad range in scope (e.g., insurance, bonding, litigation, operations, economic, etc.), we settled on the following definition:

> *"Risk management for projects in the construction industry consists of a process where risks are identified and quantified, and opportunities for mitigation are discovered. Owners involved in construction will make decisions about how to mitigate risks, which may include elements of accepting, reducing, sharing, transferring, or avoiding the risk. Ultimately, risk management involves the implementation of the mitigation plan."*

FMI/CMAA designed the survey in order to develop a basic understanding of how owners today, including those in Life Sciences, are managing risk in construction projects. In order to accomplish this, we set out to understand owner behavior when faced with a given set of risks. FMI and CMAA believe owners make risk mitigation decisions in their capital construction programs according to the degree of assumed own-

Figure 1. Risk mitigation decision matrix.

ership and the selection of a passive or active risk management approach. These decisions fall within a two-by-two matrix as proposed in Figure 1.

"Recognize and Ignore" and "Accept and Manage" are categories where the risk management strategies, tactics, or processes employed result in a high degree of ownership exhibited by the owner. Risks that owners perceive as difficult to influence, including security requirements or energy prices, are typically recognized and ignored. In extreme cases, this risk can destroy a project. Risks that are believed to be subject to influence are typically accepted and managed. These include construction management talent or estimating accuracy.

"Avoid" and "Accept and Transfer" are categories where the risk management strategies, tactics, or processes employed result in a low degree of ownership exhibited by the owner. Risks that owners perceive as severe and uncontrollable are the most actively analyzed and likely to be avoided.

"Accept and Transfer" and "Recognize and Ignore" are categories where the risk management strategies, tactics, or processes employed are more passive. In the first case, the owner pushes responsibility to actively manage the risk onto a third party. In the second case, ignoring the risk requires no action.

"Accept and Manage" and "Avoid" are categories where the risk management strategies, tactics, or processes employed are more active. In the first case, the owner actively takes on responsibility to manage the risk for his/her own account with his/her own staff. In the second case, an active investigation of the risk indicates that it is severe and uncontrollable and dictates the owner must take action to remove the exposure to the risk.

"Accept and Transfer" and "Accept and Manage" are opposites of one another in the owner's perspective in that the first pushes risk to an external party for active management, while

Continued on page 46.

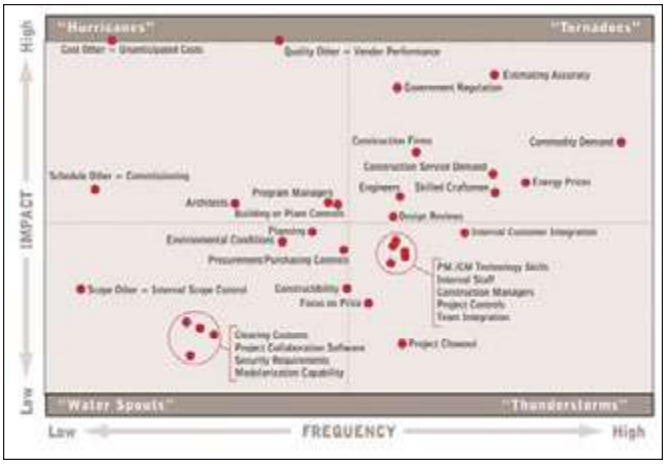


Figure 2. Frequency vs. impact aggregate scores.

the second retains the risk internally for active management.

"Avoid" and "Recognize and Ignore" are opposites of one another in the owner's perspective in that the first requires action to remove the exposure to the risk, while the second requires no action.

While owners prepare lists of known risks that may occur, research suggests that owners are reluctant to consider pessimistic scenarios while performing risk assessments.[2] These pessimistic scenarios are outside of this matrix in that they are not considered. Nassim Nicholas Taleb refers to these pessimistic scenarios as little Black Swans and he describes a set of more severe outcomes as the Unknown Unknowns or true Black Swans.

A Construction Black Swan

The Tacoma Narrows Bridge was one of the most spectacular failures in engineering history. This suspension bridge used a stiffened-girder design rather than the customary and necessarily deeper open truss. This innovative design gave a slender silhouette whose appearance was dramatic and graceful, albeit inappropriate for the site conditions. The last spectacular undulating motions of the roadway being twisted to destruction were recorded on newsreel film even as engineers were trying to understand the phenomenon of its aerodynamic instability.

Othmar Ammann, designer of the George Washington and other monumental bridges wrote:

> *"...the Tacoma Narrows bridge failure has given us invaluable information…It has shown [that] every new structure which projects into new fields of magnitude involves new problems for the solution of which neither theory nor practical experience furnish an adequate guide. It is then that we must rely largely on judgment and if, as a result, errors or failures occur, we must accept them as a price for human progress.*[3]"

The possibility of failure of the Tacoma Narrows Bridge because of a steady crosswind of 42 miles per hour was unforeseen by its designers. Nassim Nicholas Taleb refers to this as tunneling[4] or "we focus on a few well-defined sources of uncertainty... at the expense of the others that do not easily come to mind."

If the designers of the Tacoma Narrows had known the story of the Wheeling Suspension Bridge, the longest span in the world when it was completed in 1849, they would have anticipated that wind could be a possible cause of failure. The Wheeling bridge was destroyed in a storm. In this older incident, the technical literature on the design and ultimate failure of this bridge was not well-documented even though a local reporter made detailed observations of the bridge as it experienced similar undulation, due to relatively modest crosswinds.

Survey Results

Risks

A meaningful discussion about program and project-level risks is undertaken in the context of the perceived frequency and impact of that risk. There are hundreds, if not thousands, of possible risks that an owner may face when managing a construction project or program. A considerable effort was made to narrow the list of risks based on the idea that owners tend to focus on what they have previously experienced as opposed to what they have not experienced. Said a different way, owners manage the risks they know as opposed to what they do not know. FMI selected 28 specific risks and an additional four respondent-chosen risks which were tied to four areas of impact to the owner: 1. Quality, 2. Cost, 3. Schedule, and 4. Scope.

Respondents were asked to define any other risks that impact them in the areas of quality, cost, schedule, and scope. FMI selected a name for these risks based on frequency of mentions: Quality Other = Vendor Performance, Cost Other = Unanticipated Costs, Schedule Other = Commissioning or Turnover, and Scope Other = Internal Scope Control.

In Figure 2, FMI plotted each of the original 28 risks along with the four self-described risks into quadrants describing their perceived frequency and impact. High-frequency and high-impact risks are referred to as "Tornadoes." Nine risks fall into this quadrant with governmental regulation, inaccurate budgeting or estimating by the owner, and commodity demand exhibiting the combined highest frequency and severity. Risks in which the perceived frequency was high and impact was low are referred to as "Thunderstorms." Nine risks fall into this quadrant with internal customer integration representing the greatest frequency and one of the highest impacts in this quadrant.

Risks in which the perceived frequency was low and impact was low are referred to as "Water Spouts." Eight risks fall into this quadrant with a group of four, including Clearing Customs, Project Collaboration Software, Security Requirements, and Modularization Capability, perceived as exhibiting little impact. There can be two explanations for the perception of both low impact and frequency: 1. These risks actually result in an insignificant impact or 2. The assessment of impact is incomplete. As described previously, the fact that a particular risk is perceived as having low impact

is not the same as saying it cannot have high impact – we must see the forest *and* trees for success, recognizing that the most devastating risks will originate from the forest which is harder to see and discuss. Risks in which the perceived frequency was low and impact was high are referred to as "Hurricanes." Six risks fall into this quadrant with two exhibiting major or immense impacts, Cost Other = Unanticipated Costs and Quality Other = Vendor Performance. In Figure 2, these two risks are not depicted to scale and exhibited an impact twice as high as estimating accuracy.

Highest-Impact Risks

FMI studied how each risk impacted overall project success through the three basic attributes of the job: cost (financial), time (schedule), and qualitative (e.g., quality, reputation, and safety) areas. Participants were asked to score each attribute as either not applicable, no impact, minimal impact, moderate impact, major impact, or immense impact.

Each risk was ranked from the highest to lowest total impact for each attribute, and this is shown in Figure 3. For each risk, the bar length represents perceived severity (e.g., estimating accuracy is perceived to have a major reputational impact, moderate quality impact, and minimal safety impact). For example, the risk of Cost Other = Unanticipated Costs ranks the highest in both Financial and Schedule impacts, whereas Quality Other = Vendor Performance ranks the highest in Schedule impacts. Impacts to the schedule

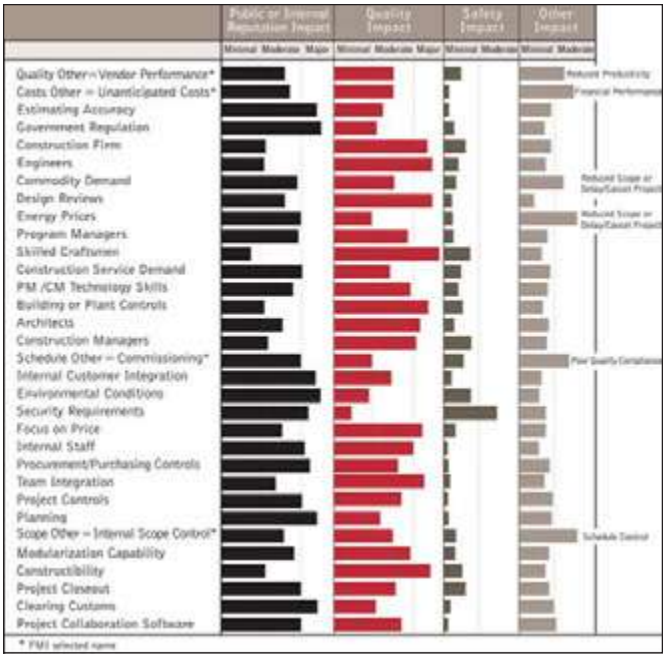


Figure 3. Qualitative impacts for each risk.

were twice as high (bad) on average as the financial impacts and the qualitative impacts. Therefore, schedule impacts proportionately influenced the total overall impact rank.

Schedule impacts are damaging because in some cases,

Continued on page 48.

Risk Category	Financial Impact Rank	Schedule Impact Rank	Qualitative Impact Rank	Total Impact Rank
Quality Other = Vendor Performance	2	2	1	1
Cost Other = Unanticipated Costs	1	1	2	2
Estimating Accuracy	3	4	3	3
Government Regulations	14	3	4	4
Commodity Demand	4	6	7	5
Construction Firm	8	8	5	6
Construction Service Demand	13	7	12	7
Energy Prices	5	10	9	8
Schedule Other = Commissioning	21	5	17	9
Skilled Craftsmen	7	14	11	10
Engineers	12	15	6	11
Program Managers	17	12	10	12
Architects	6	9	15	13
Building or Plant Controls	9	11	14	14
Design Reviews	10	19	8	15
Planning	25	13	26	16
Internal Customer Integration	22	17	18	17
Construction Managers	11	22	16	18
Environmental Conditions	24	16	19	19
Project Controls	15	20	25	20
Focus on Price	19	21	21	21
Internal Staff	18	18	22	22
PM/CM Technology Skills	20	25	13	23
Team Integration	16	23	24	24
Scope Other = Internal Scope Control	26	24	27	25
Procurement/Purchasing Controls	27	26	23	26
Constructibility	23	27	29	27
Modularization Capability	28	29	28	28
Security Requirements	29	31	20	29
Project Collaboration Software	30	28	32	30
Project Closeout	31	30	30	31
Clearing Customs	32	32	31	32

Table B. Impact ratings for each risk.

there is little that can be done by a project manager to rescue a project once a major schedule delay occurs. These delays cannot be easily resolved with a scalar approach, such as requesting a budget increase.

Participants were further asked to identify the specific qualitative impact type as either Public or Internal Reputation, Quality, Safety, or Other as a self-selected impact. This is shown in Table B. The risk with the largest public or internal reputation impact is government regulation. The risk with the largest quality impact is an inability to find or attract sufficient and trained skilled craftsmen, and the risk with the largest safety impact is, not surprisingly, security requirements.

An example of public perception impacts is the scenario of constructing highly pressurized lines snaking under farms and past residential areas. This will raise fears about safety and environmental impacts in communities along these pipeline routes. Companies building pipelines face lawsuits, eminent-domain battles, and jurisdictional fights among the local, state, and federal authorities that oversee the projects. Two New England projects have been held up or canceled in recent months because of local opposition.[5]

Skilled craftsmen carries the highest quality impact potential. Kenneth D. Simonson, chief economist for the Associated General Contractors of America, said, "To the extent that people are picking college, they're turning down construction.[6]"

Risks rated with a combination of low frequency and impact may represent potential for Black Swan-type events. Figure 4 displays a select list of low-frequency and low-impact risks (Water Spouts) from Figure 2 and breaks down the frequency of observation for each type of owner. Public and private entities make up nearly 75 percent of the frequency rating of clearing customs risks. Put another way, government agencies do not observe clearing customs issues, which suggests that their projects source materials and equipment domestically.

Modularization capability (capital construction program at risk due to inexperienced modularization installation contractor) scored 38 percent of the impact by respondents (firms) with the average project size of $15 million to $50 million. Meanwhile, projects between $100 million and $500 million expect to see 40 percent of the impacts related to project collaboration software (capital construction program at risk due to ineffective use of project collaboration software) than any other risk. Many owners reported that they also would like to convince their Procurement and Legal departments of the benefits of a collaborative delivery method to improve risk management.

Engineering News Record[7] reports that many are fearful of the transition to Building Information Management (BIM), outlining a long list of possible and increased exposure. FMI's *Eighth Annual Survey of Owners*;[8] however, concluded that

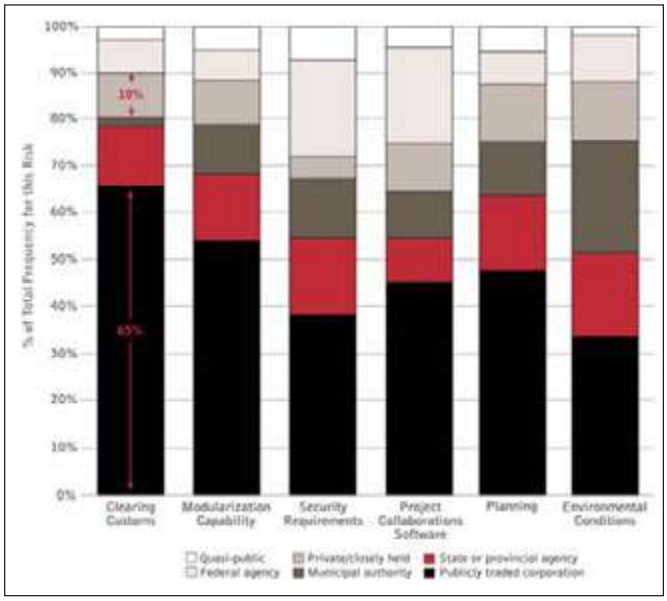


Figure 4. Percent of risk observation frequency by organization type.

Continued on page 50.

ARE YOU RELYING ON SAFETY PRODUCTS THAT *"SHOULD"* WORK?

FIKE IS COMMITTED TO RELIABLE SAFETY SOLUTIONS THROUGH RESEARCH, NEW TECHNOLOGIES, AND EXTENSIVE TESTING.

EXPLOSION PROTECTION • PRESSURE RELIEF • TESTING SERVICES

- Comprehensive selection of ASME, CE and 3-A rupture/bursting discs
- High performance explosion vents, specifically designed for sanitary applications
- Complete line of products designed for CIP/SIP applications
- Dedicated Team of Combustion Engineers and Pressure Relief Experts

DON'T LEAVE THE SAFETY OF YOUR BUSINESS TO ANYTHING LESS THAN THE MOST RELIABLE, PROVEN PRODUCTS.

EXPLOSION VENTING

EXPLOSION SUPPRESSION

RUPTURE DISCS

FULL-SCALE TESTING

Fike®

WWW.FIKE.COM

PROVEN PERFORMANCE, QUALITY AND RELIABILITY FOR OVER 60 YEARS

1-866-758-6004

"…we have to manage the risk that our knowledge will find its way into our competitors' hands through the use of foreign-based consultants, engineers, and contractors."

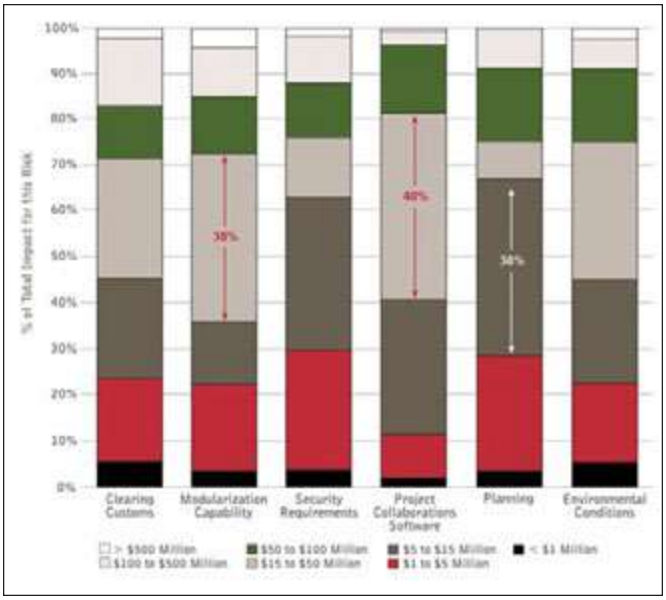


Figure 5. Percent of impact of select risks by average project size.

approximately "35 percent of all respondents have used BIM processes and technology to reduce the frequency and severity of loss." Interestingly, projects between $5 million and $15 million perceive 38 percent of the impacts as a result of planning (capital construction program at risk due to no or ineffective use of pre-project, resource, and short-interval planning techniques) than any other respondent's average project size. Projects in this range may experience major or immense cost and schedule impact if the scope changes dramatically. This is described further in Figure 5.

One participant at a large chemical company was quoted describing a risk that often goes overlooked in today's design and construction environment: "Import/export refers to protecting intellectual property and technology. This wasn't an issue 20 years ago, but we have to manage the risk that our knowledge will find its way into our competitors' hands through the use of foreign-based consultants, engineers, and contractors."

Strategies, Tactics, and Processes

The strategies, tactics, and processes are included in the mitigation plan for each risk, along with ownership assignment, costs, and timing. Unique strategies for mitigating capital project risk likely number in the hundreds. When respondents were asked which strategies they use most often, they integrate risk into contracts 74 percent of the time, while requiring an equity involvement only 10 percent of the time. This trend should continue as traditional financing is harder to obtain and Public Private Partnerships (P3) become more acceptable. Figure 6 demonstrates that owners continue to transfer risks to service providers through contractual mechanisms and language more frequently than any other approach. Using a standardized process or approach was the second most popular method at 71 percent of the time. Owners could select and apply more than one strategy at a time.

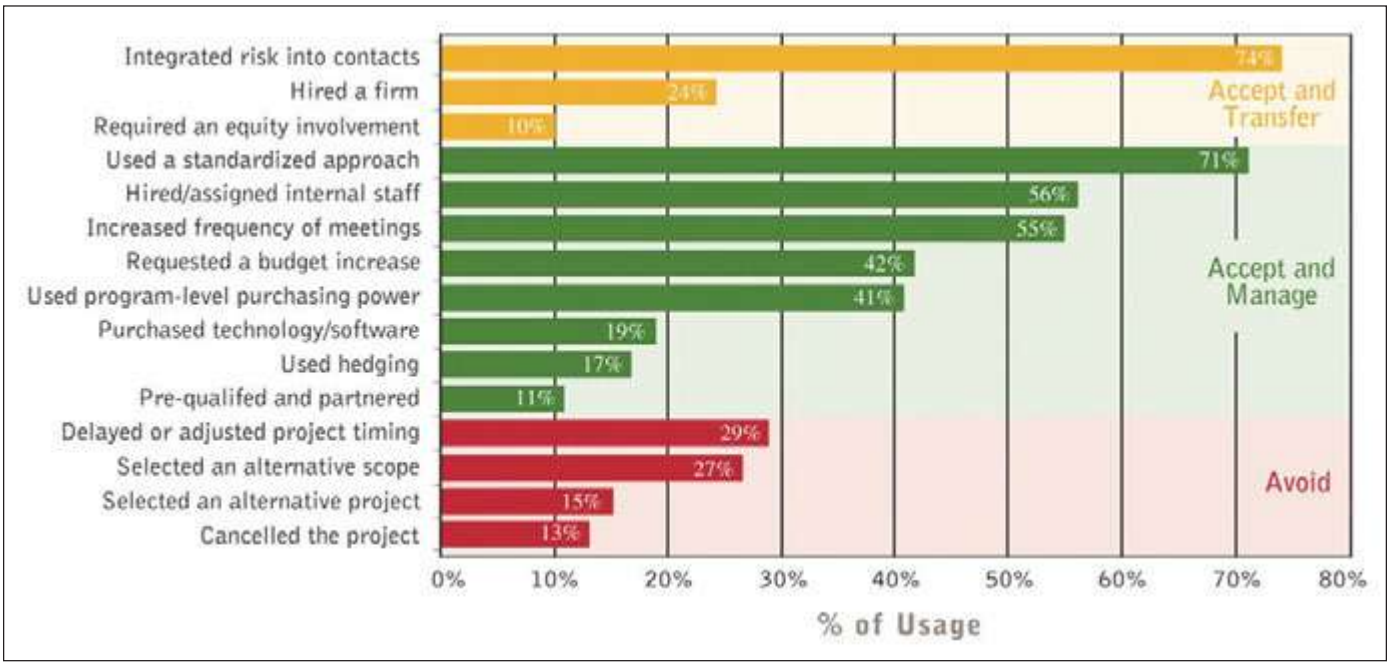


Figure 6. Ratio of usage of strategies, tactics and processes.

Continued on page 52.

DeltaV Batch.

The perfect cup. Every time.

Easy.

Emerson understands your need to quickly respond to varying customer requirements. That's why we designed DeltaV Batch to give you the robust, repeatable performance that lets you assure your customers of a perfect, on-spec batch. First time. Every time. Easy.

From seamless integration with your enterprise planning and manufacturing execution systems to modular, class-based configuration and integrated change management, DeltaV Batch simplifies your batch operations.

Enabling agile manufacturing has never been easier. So, grab yourself a fresh cup and visit: **EasyDeltaV.com/Batch**

DeltaV™

EMERSON™
Process Management

EMERSON. CONSIDER IT SOLVED.™

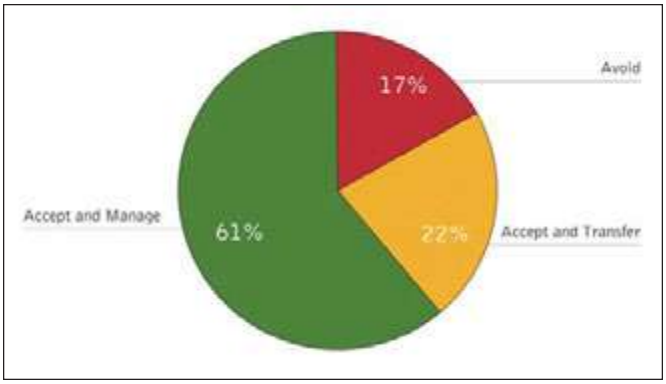


Figure 7. Choice of strategy.

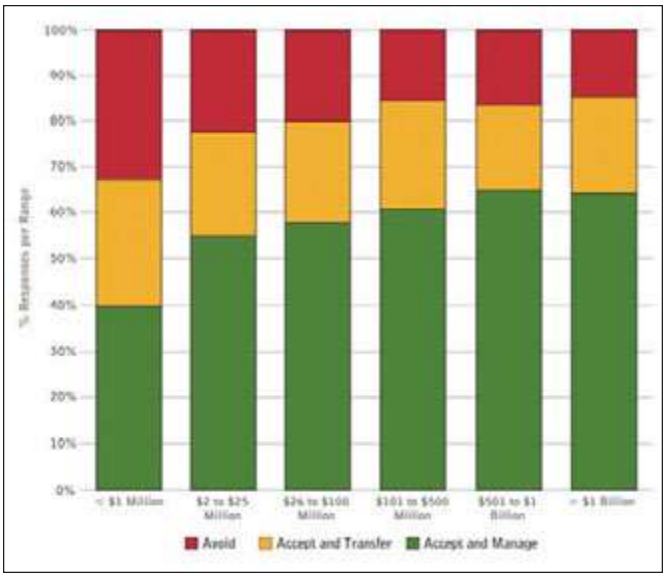


Figure 8. Strategies used by capital program size.

FMI/CMAA found that on average, 61 percent of the time owners are accepting and managing risks, 22 percent of the time owners are accepting and transferring risks, and the balance of time they avoid risks as shown in Figure 7.

Figure 8 indicates an increasing desire to manage risks internally by the owner as the size of the capital program increases. Owners with less than $1 million spending manage their own risks 40 percent of the time, whereas owners that exceed $1 billion spending tend to accept and manage risks 65 percent of the time. This trend also parallels declining appetite to avoid risks. Owners become less likely to avoid a risk as their budget for capital projects increases. This suggests that owners with large capital programs are seeking larger returns and are more willing (or blind) to subject themselves to the risks inherent in these types of projects.

Each survey participant was categorized by FMI into one construction type to analyze his/her approach to risk management by this construction type. The segregation ignores the fact that many owners complete construction of multiple types in the same project (e.g., a typical life sciences facility might have both laboratory and commercial building space). Figure 9 shows that financial, real estate, and government types of construction all take a more conservative approach to risks and avoid them as a preferred strategy. Real estate and sports-oriented projects tend to transfer risks more often than other types of strategies. These types of projects are frequently one-time interactions between owner, designer, and contractor, and pushing risk to another party has minimal long-term consequences for the owner. In the case of owners who have programmatic work year in and year out, the more aggressive movement of risk to other parties tends to have more severe consequences. Life Sciences participants tend to Accept and Manage risks to the same extent as other process-intensive industries, such as Chemical, Energy, and Manufacturing.

Strategies to Mitigate Risks

Participants in the survey were not directly asked how they addressed each risk. The results in this section are derived from statistical correlations of the risk frequencies, risk impacts, and use of particular risk mitigation strategies. We studied how owners react to risks based only on 1. The frequency of occurrence and 2. The potential impact that the risk would have upon their program. Participants also were not asked about any particular strategies related to ignoring risks because it is assumed that if an owner ignores a risk, no strategy, tactic, or process is used to mitigate it; thus, measurement would not be feasible. The results were inferred by low correlation coefficients associated with the other three classifications. Refer to Figure 10 and Figure 11 for this analysis.

The top strategies, tactics, or processes that were most consistently applied to address a particular risk are shown in

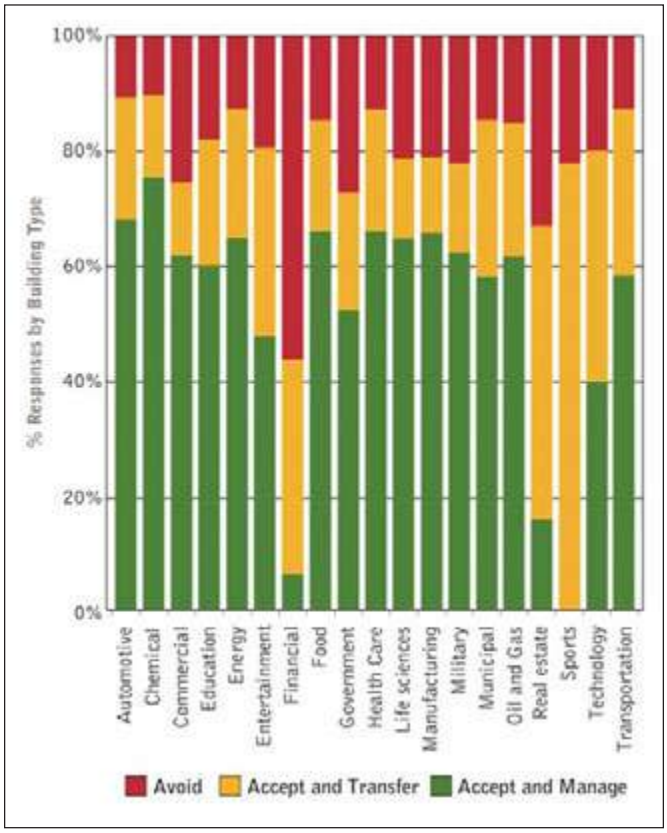


Figure 9. Strategic action by building type.

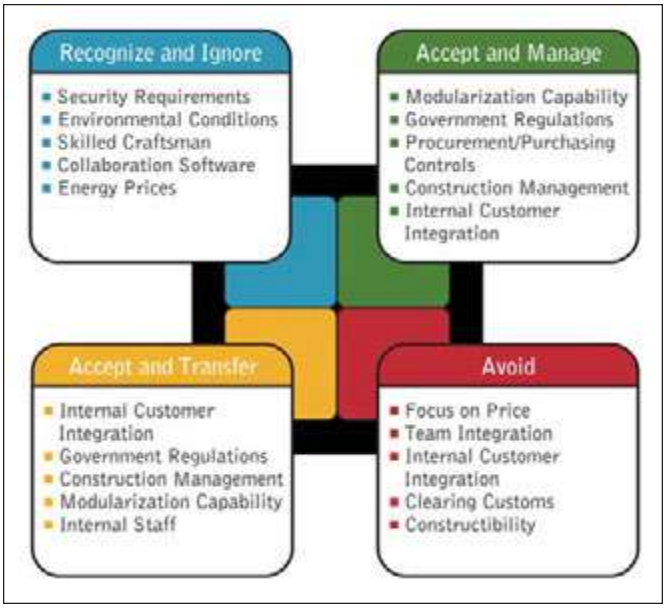


Figure 10. Connecting strategies and risks based on frequency of occurrence.

Table C. The risks that were originally scored as low frequency and low impact are italicized for emphasis. For example, owners that delay or adjust the timing of a project seem to do so when they are experiencing a risk due to an inability to attract qualified internal staff.

In 11 out of 32 risks evaluated in the survey, requesting a budget increase was the most employed strategy, tactic, or process – throwing money at the challenge. If project directors know that the tactic of getting more money is an accepted practice, they are going to be less concerned about cost-related impacts from risks. This explains the observation made in connection with Table B in which schedule impacts are of more concern to owners than financial and qualitative impacts.

Strategy, Tactic, or Process	Most Often Applied to Address These Risks
Selected an Alternative Scope	*Planning*
Requested a Budget Increase Team Integration Estimating Accuracy *Environmental Conditions* Project Closeout Government Regulations Focus on Price Constructibility Design Reviews Internal Customer Integration	Energy Prices
Cancelled the Project	Building or Plant Controls
Delayed or Adjusted Project Timing	Architects Internal Staff PM/CM Technology Skills *Clearing Customs*
Used Hedging	Construction Demand
Used Program-level Purchasing Power	Engineers Skilled Craftsmen Construction Firms Commodity Demand *Project Collaboration Software* Project Controls *Modularization Capability*
Purchased Technology/Software	Procurement/Purchasing Controls
Increased Frequency of Meetings	Program Managers Construction Managers *Security Requirements*

Table C. How specific risks are addressed.

Concluding Thoughts

Innovative owners, progressive corporate boards, and highly engaged capital construction teams are injecting risk management discussions routinely into their capital planning. FMI and CMAA believe this type of assertiveness is necessary across the industry and unfortunately too rare. The pace of change, design challenges, and financial complexity makes the process of capital construction higher risk and more challenging even for the most sophisticated owners. As reported earlier, 30 of 32 risks presented in this study were rated with multiple "Immense" impacts indicating catastrophic or Black Swan-type occurrences. Corporate boards now consider the "worst things" that could happen as a method of being engaged and monitoring the business risks.[10] CMAA and FMI are driving the industry toward this higher level of engagement. Use of a Certified Construction Management (CCM) professional, selection of aligned and efficient project delivery systems, and industry training in leadership and management are just three examples of how FMI/CMAA support this transformation.

Concludes on page 54.

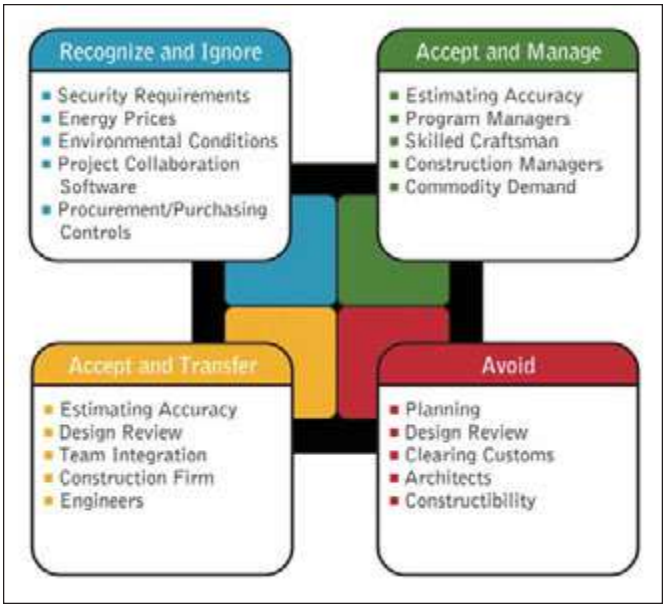


Figure 11. Connecting strategies and risks based on the potential impact.

More can be done and we believe successful owners will move "beyond the bell curve" in risk management of their projects. These efforts will recognize and take into account the following:

- History is less applicable today because complexity is changing the nature of the game.
- The most immense and severe impacts to capital construction programs are unpredicted, one-time events.
- Black Swan-type events will take place and recognizing their range of impact is more critical than attempting to predict when they might occur.
- Work to specifically avoid underestimating the impact and likelihood of improbable events and understanding the nature of more frequent risks.
- Focus on the "forest" as the source of the most devastating risks while managing the "trees" which are easier to see and discuss.

References

1. Nassim, Nicholas Taleb, Adapted from *The Black Swan (The Impact of the Highly Improbable)*, Random House, 2007, pg 50.
2. Touran, Ali, "Owners Risk Reduction Techniques Using a CM," Department of Civil and Environmental Engineering, Northeastern University, August 2006. CMAA-sponsored research.
3. Petroski, Henry, *To Engineer is Human, The Role of Failure in Successful Design*, Vintage Books, 1992, pp. 163-171.
4. Nassim Nicholas Taleb, The Black Swan (The Impact of the Highly Improbable), Random House, 2007, pg. 50.
5. Casselman, Ben, "Expansion of Pipeline Stirs Concerns Over Safety," Wall Street Journal, August 4, 2008.
6. Troianovski, Anton, "Skilled Trades Seek Workers," Wall Street Journal, August 19, 2008.
7. Speed, Vicki, "Strategies for Managing Risk in a New Era of Project Delivery," Engineering News Record, March 31, 2008.
8. FMI/CMAA *Seventh Annual Survey of Owners; C2 + 2C = LC, The Solution to Low Cost Capital Programs*, Fall 2006 publication, pp. 1-3.
9. FMI/CMAA *Sixth Annual Survey of Owners*, Fall 2005 publication, pg. 15.
10. Lublin, Joann S. and Tuna, Cari, "Anticipating Corporate Crises: Boards Intensify Efforts to Review Risks and Dodge Disasters," Wall Street Journal, September 22, 2008.

About the Authors

Jeff Lukowski has more than 15 years of experience in project planning and execution, manufacturing and process development in both the life sciences and chemical industries. He is a consultant with FMI Corporation specializing in streamlining capital construction programs for owners in the highly-engineered industries of chemical, life sciences, and utility/power generation. While improving performance of owner's construction organizations through standardization and process improvements, he also helps engineers, contractors, and vendors/suppliers identify new market opportunities. He has a BS in chemical engineering and a BS in environmental engineering from Michigan Technological University and a MBA from the University of North Carolina – Kenan Flagler Business School. He also is a Professional Engineer in the state of Michigan and a member of the ISPE Project Management Community of Practice. He can be contacted by telephone: +1-919-785-9213 or by email: jlukowski@fminet.com.

Mark Bridgers is a senior consultant with FMI and works with owners or purchasers of construction contracting services in the areas of organizational analysis, construction cost management, accounting and financial issues, and strategy development. He brings more than 15 years of construction industry expertise, including financial engineering, surety bonding, and reinsurance experience to FMI. He consistently implements cost-saving innovations and strategies for his owner clients, including building strong supplier relationships to manage the risks of low quality and diminishing craft labor. Bridgers holds a MBA from the University of Virginia's Darden School and a Bachelor's in financial management from Clemson University. He has earned the titles of Chartered Property and Casualty Underwriter (CPCU) and Associate in Reinsurance (ARe). He can be contacted by telephone: +1-919-785-9351 or by email: mbridgers@fminet.com.

FMI Corporation, 5171 Glenwood Ave, Suite 200, Raleigh, North Carolina 27612, USA.

This article presents a fundamental understanding and practical application of bacterial adhesion, the first step leading to infections. This article specially focuses on two cases, cranberries and urinary tract infections, and implanted biomaterial infections.

Fundamentals of Bacterial Adhesion Applied Toward Infection Prevention: Focus on Two Case Studies

by Yatao Liu, Paola A. Pinzon-Arango, Joshua Strauss, and Terri A. Camesano

First presented by Yatao Liu at the 2007 ISPE Boston Chapter Student Poster Competition where he won the Graduate Level award, this research was then presented at the ISPE International Student Poster Competition in Las Vegas, NV later that year.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2009,
Vol. 29 No. 1

Introduction

Bacterial infections persist as a public threat due to the ease by which bacteria adapt to commonly used antibiotics. Traditional antibiotics are effective against multiplying bacteria that are planktonic (free floating). However, bacteria on surfaces develop protective communities called biofilms that hinder the ability of antibiotics to completely eliminate the pathogens. The rapid development of bacterial resistance to antibiotics has made pharmaceutical companies reluctant to fund new antibiotics research. Hence, novel approaches to prevent and treat infections are needed. One promising strategy is to control the first step of bacterial adhesion, thus preventing infection. Our work combines experiments and modeling aimed at understanding the initial steps of the bacterial adhesion process, focusing on two case studies: 1) mechanisms by which cranberry can prevent urinary tract infections through interfering with bacterial adhesion; and 2) design of anti-adhesive and antimicrobial coatings for biomaterials. We make direct adhesion force measurements between bacteria and substrates with an Atomic Force Microscope (AFM), and combine such experiments with thermodynamic calculations to develop a set of tools that allows for the prediction of whether bacteria will attach to a given surface. These fundamental investigations of the bacterial adhesion process help elucidate the underlying mechanisms behind bacterial adhesion, thus leading to improved clinical outcomes for a number of biomedical applications.

Bacterial Adhesion is the First Step in Infection Development

As one of the earliest life forms, bacteria have evolved into many thousands of species and can survive in a wide range of environments. According to National Institutes of Health (NIH), fewer than one percent of bacterial species can cause disease with most bacteria being harmless or even beneficial to humans, such as bacteria residing in human intestines that help digest food[1] or cultures that contribute to the fermentation processes of yogurts and cheeses. Despite the fact that most bacteria are not pathogens, infectious diseases claim 1,500 deaths per hour worldwide.[2] Bacterial infections that lead to pneumonia, tuberculosis, and severe diarrheal diseases, along with infectious agents of malaria, measles, and HIV/AIDS, account for half of all premature deaths worldwide, especially affecting children and young adults.[2] Due to antibiotic resistance, some infections cannot be cured by conventionally prescribed antibiotics. For example, nearly 19,000 people died in the United States in 2005 after being infected with methicillin-resistant *Staphylococcus aureus* strains that have spread rampantly through hospitals and long term care facilities.[3]

The increasing public health crisis caused by bacterial resistance necessitates alternative approaches to preventing and curing infections. The initiation of a bacterial infection requires that bacteria first attach to host tissue. The attachment of bacteria to a surface is typically described as occurring through two stages: long range, non-specific forces help the bacterium make a close contact with host cells or a substratum, where stronger specific forces can become operative. Once attached, bacteria grow, secrete extracellular material, and can develop a biofilm, which is a dense and protective community of microorganisms.

The initial adhesion process is considered to be governed by specific and non-specific inter-

action forces between bacteria and substrata. Non-specific interactions typically refer to 1. Lifshitz-van der Waals (LW) forces that are almost always attractive and operate between any two bodies 2. electrostatic interactions, which are often repulsive because bacteria and many surfaces each possess negative charges, and 3. electron-donor/electron-acceptor or Lewis Acid/Base (AB) forces, which include hydrogen bonding. Specific forces, which are much stronger, refer to bonds between ligands and receptors of two biological samples. We discuss our approach to modeling and measuring the forces involved in the initial bacterial adhesion process.

Methods in Studying Bacterial Adhesion

Bacterial adhesion can be studied at various scales, from macroscale studies that show the adhesion behavior of a population of bacteria, to nanoscale studies that probe individual cells or molecules associated with bacteria. Although macroscale studies are phenomena-oriented, they cannot provide information needed to disclose the underlying mechanisms. A combination of studies at different length scales can provide a more detailed picture.

Direct Force Measurements

Interaction forces between bacteria and host cells or implanted medical devices directly determine whether bacteria will adhere. Although the quantification of adhesion forces between bacteria and a substrate represents the most accurate and straightforward way of gaining information on bacterial adhesion, in practice, there are two crucial issues that need addressing.

Tiny Forces

The interaction forces between bacteria and a substrate are very small with values typically at the pico-Newton (pN) to nano-Newton (nN) scales, i.e., (7-70) × 10^{-12} lb·ft/s^2. Currently, only two techniques can be used to directly detect such forces. One is optical tweezers[4] and the other is atomic force microscopy (AFM).[5, 6, 7] AFM provides larger measurement range and more sophisticated controls, such as the loading rate, in addition to providing simultaneous high resolution imaging - *Figure 1*. There are additional indirect techniques used to estimate the interaction forces. These techniques include Total Internal Reflection Microscopy (TIRM), Total Internal Reflection Aqueous Fluorescence (TIRAF) microscopy, Surface Forces Apparatus (SFA), and Quartz Crystal Microbalance with energy Dissipation (QCM-D), etc. Interested readers are encouraged to refer to a comprehensive review paper on the use of these techniques in bacterial adhesion studies.[8]

Obtaining Correct Orientations of Biological Molecules

In order for bacterial ligands to correctly bind with receptors, the molecules on bacterial surfaces, including fimbriae (pili),

Continued on page 58.

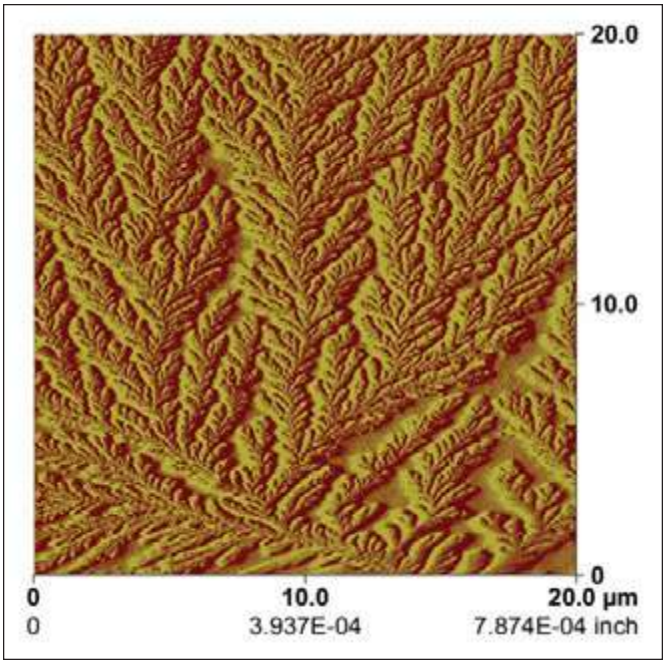


Figure 1. Representative AFM amplitude imaging of the deposition of *E. coli* culture solution after washed three times with phosphate buffer saline. Then the solution was deposited onto a mica surface. They formed a tree-like crystallization.

and lipopolysaccharides, must expose the appropriate orientation. Experimentally, it is challenging to maintain correct orientation when biological cells are trapped in optical tweezers or immobilized on an AFM tip. In our lab, we invented a novel coating method that can be used to attach bacteria to an AFM tip (Figure 2), such that they possess the correct orientation for direct force measurements.[9]

Some technical issues also need to be resolved in force measurements such as the timescale and loading rate. The timescale needed to build a ligand-receptor bond can be difficult to determine. Further, the loading rate needed to make AFM force measurements has to be specified for each experiment. These parameters should be appropriately determined to obtain correct force measurements.

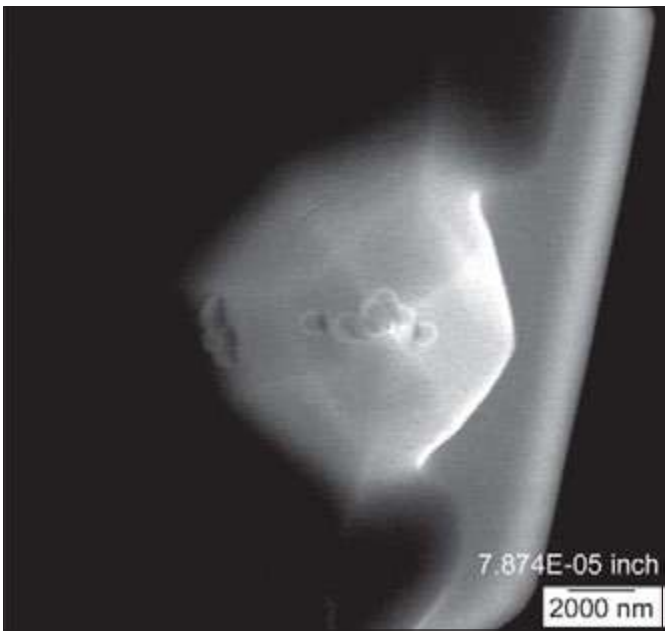


Figure 2. Representative SEM imaging of *S. epidermidis* coated AFM tip.

Thermodynamic Modeling of Bacterial-Surface Interactions

Classical and extended Derjaguin-Landau-Verwey-Overbeek (DLVO) theory has been used to explain and predict the adhesion behavior of bacteria in aqueous media. The DLVO model takes into account van der Waals interactions, electrostatic interactions, and often includes electron donor/electron acceptor interactions when the extended DLVO model is applied. Parameters to include in the thermodynamic models need to be estimated for each bacterium, substrate, and solution. For example, zeta potential measurements on bacteria in a suspension are used for the modeling of electrostatic interactions.

Parameters for the thermodynamic calculations are taken from contact angle measurements on bacterial lawns and on the substrates of interest, using probe liquids with varying polarities. Individual surface tensions can be calculated from the measured contact angles by using the Young-Dupré equation.[10] The Gibbs free energy change due to adhesion is calculated from the interfacial tensions for bacteria/substrate, bacteria/water, and substrate/water. If bacteria can attach to a substrate, then the newly formed interface (bacteria-substrate) must be more stable than the two old interfaces (substrate-liquid and bacteria-liquid). The Gibbs free energy change during the process must be negative to favor the new interface, which represents bacteria attached to the substrata. If the Gibbs free energy change is positive, bacteria prefer to not attach to the surface, but to remain in the aqueous media. One advantage for using thermodynamic modeling is that the method is reliable for many kinds of substrates, especially when at least one non-biological surface is applied. In addition, this method has a strong and well-defined theoretical foundation, which helps to fundamentally explain bacterial adhesion and offer a theoretical guide for biomaterial development or infection-prevention strategy. However, the thermodynamic modeling only accounts for non-specific interactions. If both surfaces are biological samples, ligand-receptor interactions may be present. Then the interaction forces calculated from the thermodynamic model will be greatly underestimated, as we reported earlier.[11] A detailed explanation on the use of these models for bacterial adhesion calculations was reported in our previous studies.[11]

Macroscale Studies of Bacterial Attachment

One of the simplest ways to quantify bacterial attachment to a surface is via a retention assay. Bacteria are incubated with host cells or the biomaterial of interest; either statically or under flow conditions. After a pre-determined time, host cells or the substrata are removed and washed to remove the loosely attached bacteria. The percentage of attached bacteria that are viable can be quantified using a dual DNA staining kit, in which green and red fluorochromes can be used to discern the number of viable cells - *Figure 3*.

Although a bacterial retention assay is a quick way to screen various surfaces or treatments, it does not provide mechanistic information on why bacteria attach. In addition, it can be difficult to conduct the experiments reproducibly, particularly if bacteria aggregate, making it difficult to get accurate cell counts. Numerous trials may be required to obtain statistically meaningful data. However, this simple assay may be used as a reference method to compare with other methods of quantifying bacterial adhesion.

Case Studies

While there are numerous types of bacterial infections with varying degrees of clinical severity, we focus on two examples that our lab has studied extensively.

Case I: Cranberry as a Preventive Measure for Urinary Tract Infections (UTIs)

UTIs and Antibiotic Resistance

Urinary tract infections are defined as infections of the kidneys, ureters, bladder, or urethra and are the second most common type of infection in the US. Symptoms generally include a frequent urge to urinate, pain and burning in the area of the bladder or urethra during urination, and in some cases, fever, fatigue, and trembling. Women, infants, and elders are more prone to UTIs. Approximately one third of women will have at least one UTI in their lifetime.[12] The annual rate of infection among women in the United States is 11.3 million symptomatic cases[13] and more than 10 million asymptomatic cases.[14] The estimated annual medical expenditures are more than $1.6 billion.[15] The Gram-negative bacterium *Escherichia coli* is the main culprit, responsible for 85 to 95 percent of cystitis cases (bladder infection) and 90 percent of acute pyelonephritis cases (a serious kidney infection).[16]

Although most bacterial infections are treatable with antibiotics, bacterial resistance to currently available antibiotics has become an increasing threat to public health, largely due to inappropriate dosing and administration of antibiotics, as well as the rapid ability of bacteria to exchange genetic information that confers resistance. Cotrimoxazole (trimethoprim/sulfamethoxazole) is the current first-line treatment for uncomplicated UTIs in the US and many other countries, but cotrimoxazole resistance exceeds 15 percent and can be as high as 25 percent in Canada and the US.[17]

Cranberries and UTIs

Native Americans used cranberries as a food source, and for many years, cranberries have been experientially recognized for their benefits of maintaining urinary tract health. Preliminary clinical studies of cranberry's benefits began in the early 1920s.[18, 19] In 1994, Avorn et al. were the first to successfully demonstrate that consumption of cranberry juice reduces the frequency of recurrent urinary tract infections in a population of elderly women. Although very early studies

Continued on page 60.

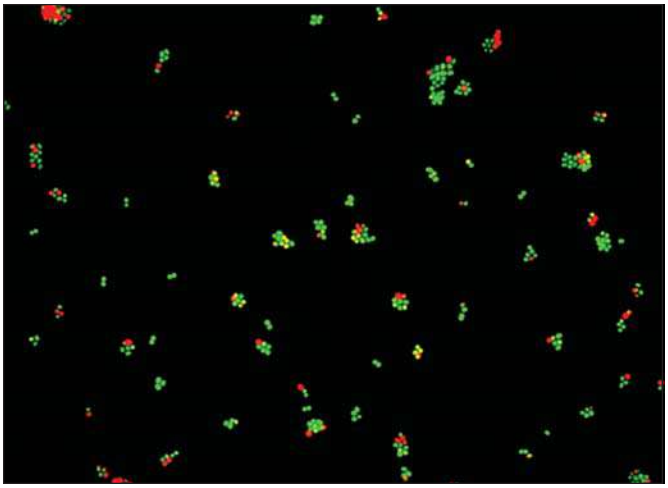


Figure 3. Representative image of *S. epidermidis* stained with live/dead kit for an adhesion assay.

hypothesized that increased acidity produced in the urine by eating cranberries was the reason for the beneficial effect,[18] more recent work has shown that the pH of urine after cranberry juice cocktail consumption only changes slightly[20] and is transient.[21]

In 1984, Sotoba et al. found that preincubation of *E. coli* and uroepithelial cells in cranberry juice decreased bacterial adhesion,[22] leading to a paradigm shift in the understanding of the action of cranberry on bacterial adhesion. Since that time, researchers have focused their efforts on gaining a detailed molecular-scale understanding of the mechanisms behind this action.

Molecular Mechanisms of Cranberries Preventing UTIs

Compounds in cranberries affect molecules on the surface of Gram-negative bacteria. For example, fimbriae are proteinaceous structures that extend from *E. coli* and contain a specific adhesin molecule (PapG) that helps the bacteria bind to a receptor on uroepithelial cells, known as the α-Gal(1→4)β-Gal oligosaccharide receptor. *E. coli* that posses P type fimbriae can cause more serious types of UTIs, such as acute kidney infection (pyelonephritis), in addition to the less severe cystitis (bladder infection). We review some of our recent work, focusing on P-fimbriated *E. coli* and a non-fimbriated mutant strain, which allowed us to better understand the role of cranberry compounds on P fimbriae.

Bacterial Retention Assay

Building upon the available clinical studies, we performed *in vitro* bacterial adhesion assays that were designed to help understand the mechanisms behind cranberry's action on the *E. coli*-uroepithelial cell interaction. Using neutralized cranberry juice so that the effects of pH on bacterial adhesion could be eliminated, we found that the number of attached *E. coli* per uroepithelial cells decreased from 50.2 ± 22.9 bacteria/uroepithelial cell without cranberry juice treatment, to 13.6 ± 5.7, 9.3 ± 4.1, and 2.9 ± 1.5 bacteria/uroepithelial cell, corresponding to 5, 10, and 27 wt.% cranberry juice treatment, respectively.[23] These *in vitro* attachment results confirmed that cranberry juice cocktail can reduce bacterial attachment to host tissue, and that lower pH is not the underlying mechanism that makes cranberry juice an effective agent for preventing UTIs.

P-fimbriae Morphology Characterization

Through Atomic Force Microscopy (AFM) measurements, together with steric modeling, we found that the average P-fimbriae length on *E. coli* HB101pDC1 was 147 nm (around 600 × 10^{-8} inch) without cranberry juice treatment, but decreased to 50 nm (around 200 × 10^{-8} inch) when bacteria were exposed to cranberry juice - *Figure 4*.[24] Thus, we directly demonstrated that although P fimbriae are not removed by exposure to cranberry juice, the proteins become compressed significantly after cranberry juice treatment, which may account for their decreased ability to adhere to uroepithelial cells.

Direct Force Measurements

In addition, AFM was used to show that the adhesion force between *E. coli* and a uroepithelial cell was ~10 nN (7.233 × 10^{-8} lb·ft/s^2) when no cranberry juice cocktail was present, but decreased to ~0.50 nN (0.362 × 10^{-8} lb·ft/s^2) after cells were exposed to 27% cranberry juice cocktail.[25] The specific adhesion forces between PapG adhesin and receptors on uroepithelial cells were significantly decreased after cranberry juice treatment. This was the first study to directly demonstrate that cranberry juice treatment reduces the nanoscale adhesion forces between bacteria and uroepithelial cells.

Thermodynamic Modeling

Through thermodynamic modeling, we showed that the Gibbs free energy change (ΔG_{adh}) between *E. coli* and uroepithelial cells in the absence of cranberry juice treatment was -20 mJ/m^2 (around -150 ft-lbs/ft^2), where the negative value implies that bacterial adhesion is favorable. With increasing concen-

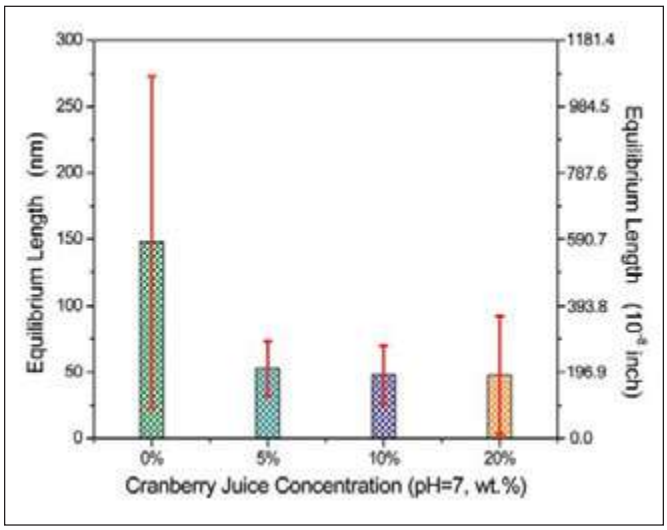


Figure 4. The average equilibrium length of P fimbriae on *E. coli* surface derived from steric modelling based on AFM surface characterizations. Adapted with permission from Liu *et al.*, *Biotechnology and Bioengineering*, 2006, **93**, 301 (Ref. 24). Copyright (2005) Wiley Periodicals, Inc.

trations of cranberry juice treatment, increased and became positive when the bacteria and uroepithelial cells were exposed to at least 20 wt. percent cranberry juice cocktail, suggesting that at or above this concentration, bacterial adhesion is unfavorable.[26] These results imply that cranberry juice can impair non-specific interactions between bacteria and uroepithelial cells and hence prevent bacterial adhesion.

Therefore, cranberry can provide protection at three different levels:

a. Cranberry juice exposure compresses P fimbriae of *E. coli*, thus preventing adhesion between the bacterium and the uroepithelial cell.

b. Cranberry juice increases the repulsive energy barrier to adhesion, over a range of hundreds of nanometers (400 × 10^{-8} inch), thus preventing the bacteria from coming into contact with the uroepithelial cells.

c. Even if bacteria are able to penetrate the repulsive energy barrier, the action of cranberry juice on the bacteria decreases the ability of the bacteria to attach to uroepithelial cells, as demonstrated through direct force measurements.

Future Directions for Cranberry Research

Although progress has been made in understanding cranberry's actions against *E. coli* toward the protection of urinary tract health, there are a number of key research issues that remain to be addressed. For example, a large body of research is devoted to identifying the critical compounds in cranberry that cause the anti-adhesive benefits, and in elucidating the needed dose and duration of exposure to such compounds. Due to the acidity of cranberry juice, commercially available cranberry juice cocktails are sweetened with fructose, water, and vitamin C, yielding 25 to 27 wt. percent cranberry juice. Therefore, there are more than 120 different compounds in cranberry juice.[27] Most research has focused on isolating and identifying the class of A-type proanthocyanidins (PACs) or non-dialyzable materials, which have shown decreases in bacterial adhesion *in vitro*.[28, 29, 30, 31, 32, 33]

However, it is not easy to translate the dose required to impart an anti-adhesion effect in an *in vitro* study to the dose needed for clinical relevance. Our *in vitro* studies showed that 5.0 wt. percent cranberry juice was sufficient to prevent bacterial adhesion[24, 25] from the molecular scale perspective for the first time although similar results were observed in prior *in vitro* bacterial adhesion assay experiments.[30, 34] Although it is not yet known how these *in vitro* thresholds will translate to *in vivo* conditions, researchers are actively engaged in trying to extend laboratory-scale mechanistic studies toward clinical trials. Increased understanding of the molecular action of cranberry juice on *E. coli* and uroepithelial cells can lead to better estimation of needed cranberry juice dose and duration.

Continued on page 62.

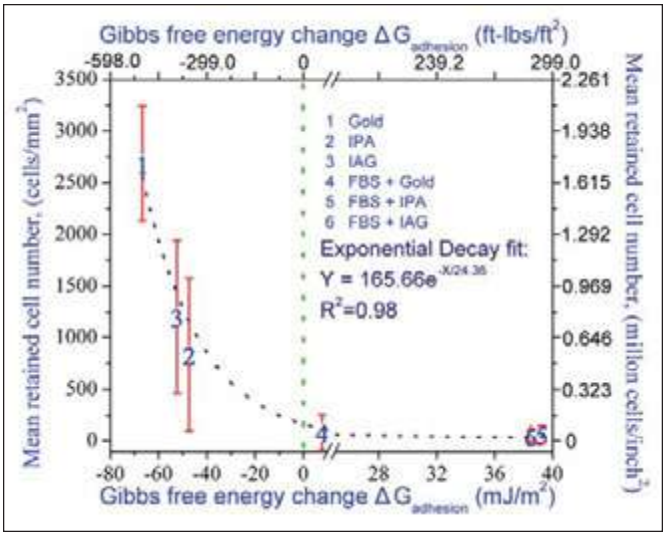


Figure 5. Correlation between Gibbs free energy change and *S. epidermidis* retention. Adapted with permission from Liu *et al.*, *Langmuir*, 2007, **23**, 7138 (Ref. 11). Copyright (2007) American Chemical Society.

Case II: Infections of Implanted Medical Devices

Infections on Biomaterials

Modern medicine is highly dependent on implanted medical devices, such as catheters, cerebrospinal fluid shunts, prosthetic heart valves and prosthetic joints, vascular grafts, cardiac pacemakers, and intraocular lenses, etc., which have significantly improved quality of treatments for patients. However, any time a foreign material is introduced into the body; this surface becomes a likely site of bacterial infection. For example, 4.3 percent of 2.6 million orthopedic implants and 7.4 percent of cardiovascular implants become infected per year.[35, 36] Bacterial infections occur in more than two million surgical cases each year in the US alone, which burdens patients both physically and financially.[37] Annually in the US, there are more than 250,000 Catheter Related Bloodstream Infections (CRBSIs).[38] The Gram-positive bacterium *Staphylococcus epidermidis* has evolved as a leading cause of nosocomial sepsis and is the most frequently isolated causal organism for infections of numerous types of catheters, shunts, and other implanted medical devices.[39, 40, 41] For example, *S. epidermidis* and other coagulase-negative *Staphylococci* were the causal agents in ~50 percent of CRBSIs.[42]

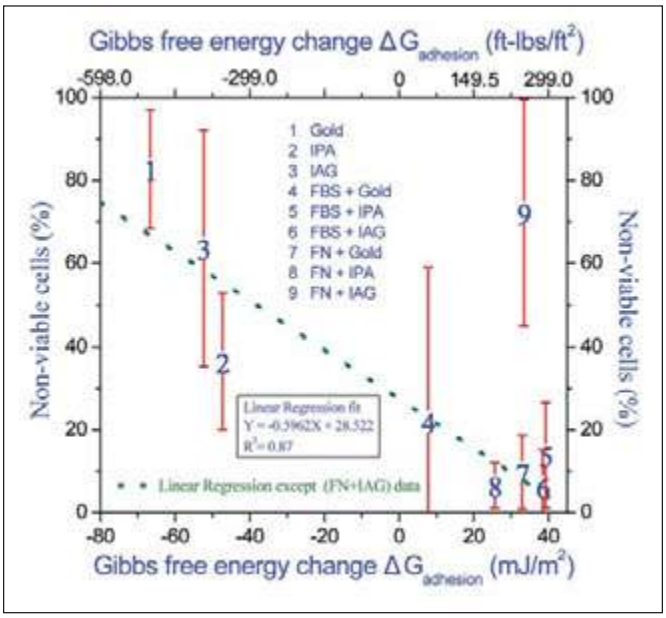


Figure 6. Correlation between Gibbs free energy change and *S. epidermidis* viability. Adapted with permission from Liu *et al.*, *Langmuir*, 2007, **23**, 7138 (Ref. 11). Copyright (2007) American Chemical Society.

Once bacteria attach to implanted medical devices, they can easily form a protective biofilm because the biofilm community is encased in a matrix of polysaccharides and proteins, which presents a diffusion barrier for antimicrobial agents' penetration. Further, the reduced metabolic rate of the bacteria in the biofilm causes a slow rate of uptake of antimicrobial agents. The biofilm also shields bacteria from environmental stresses.[43] Often the only effective treatment of an infected implanted medical device is surgical excision.[44] In addition to increasing the patient's morbidity, mortality, and recovery time, the economic expenditure on bacterial-infected medical devices exceeds $3 billion per year in the US alone.[35]

Strategies toward Preventing Implanted Medical Device Related Infections

Current research is focused on designing materials that resist bacterial adhesion or that inactivate attached bacteria. One strategy has been to coat antimicrobial agents directly onto the implanted materials to kill bacteria upon initial adhesion or as they begin to grow. A variety of antibiotics such as vancomycin, gentamicin, clindamycin, fusidic acid, ciprofloxacin, cefuroxime, cefotaxime, and chlorhexidine have been tested *in vitro* and in animal models;[45, 46, 47] however, only limited success has been obtained. The main challenge is that it is difficult to maintain a steady release of drug from the biomaterial. The focus of several research groups, including ours, is to develop materials that resist the adhesion of bacteria to surfaces. Coatings such as Self-Assembled Monolayers (SAMs) and polymers have demonstrated the ability to prevent bacterial adhesion by modifying surface properties such as hydrophobicity, roughness, and surface charge.[7, 48, 49] However, bacterial adhesion results do not show consistent trends in terms of the physicochemical properties of the surfaces. For example, we showed that surface wettability and roughness were insufficient properties to correlate with bacterial adhesion.[7] A better ability to characterize the properties of biomaterials at the molecular level may lead to better design of antibacterial biomaterials.

Use of Self-Assembled Monolayers (SAMs) to Create Anti-Adhesive Coatings

SAMs possess a layer of molecules with the same terminal group and uniform orientation, properties that facilitate the study of bacterial adhesion since bacteria are always exposed to the same chemical groups. In our laboratory, we developed a series of SAMs with varying terminal groups that were designed to resist bacterial adhesion and/or inactivate bacteria. The two most promising candidates we identified were

dodecanethiol-based SAMs (terminating in isophthalic acid or isophthalic acid with silver). The silver-containing SAMs were of interest because the antibacterial properties of silver have been demonstrated, and bacteria are unable to develop a resistance to silver's antimicrobial abilities.[50] In addition, silver has been shown to be nontoxic to mammalian cells at similar concentrations.[51]

When evaluating the potential of an antibacterial coating for a particular biomaterial, it is also important to consider how serum and plasma proteins, such as fibronectin, laminin, fibrin, and albumin will adsorb to the biomaterial. In our work, we also tested the adsorption of model proteins (fetal bovine serum and fibronectin) to the SAM-coated materials.

We found that the attachment of *S. epidermidis* to the protein-coated material depended on the particular protein present. Fetal bovine serum adsorption reduced the attachment of *S. epidermidis* to the material, while fibronectin coating promoted *S. epidermidis* attachment.[52]

SAMs terminating in Isophthalic Acid (IPA) and Isophthalic Acid with silver (IAG) resulted in lower non-specific adhesion forces with *S. epidermidis* compared to bare surfaces, as supported by thermodynamic modeling. When serum proteins were adsorbed on the SAMs, non-specific interactions between the bacteria and substrate decreased - *Figure 5*. While the LW forces were unchanged, AB forces were found to dominate the overall interaction, and showed more variability in terms of the type of SAM and protein put on the substrate. Since AB forces mainly reflect hydrogen bonds, we suggest that a fruitful approach to enhanced development of antimicrobial biomaterials would be to select materials that prevent or limit the formation of hydrogen bonds.[11]

The thermodynamic modeling was supported by direct AFM force measurements between an *S. epidermidis*-coated AFM tip and the various SAMs or protein-coated surfaces. Stronger adhesion forces were observed between *S. epidermidis* and fibronectin than between the bacteria and fetal bovine serum, due to the formation of strong ligand-receptor bonds that can only occur with fibronectin.[53] Since protein coatings can mask the underlying surface properties, it is important to consider the competition between *S. epidermis* and serum protein for adsorption to the biomaterial.

In our study, the IPA-terminating SAM showed the best activity in terms of preventing bacterial adhesion and inactivating bacteria. IAG showed strong anti-bacterial adhesion properties similar to IPA. In addition, IAG killed around 60 percent attached *S. epidermidis*[11] - *Figure 6*. IAG coated with a protein layer of more than 100 nm (3.94×10^{-6} inch) still was able to present antibacterial activity since we assume some silver ions could diffuse through the protein layer. However, when the protein coating was thicker than 250 nm (9.85×10^{-6} inch), the ability of the SAM to inactivated bacteria decreased significantly.[52] These results emphasize again that bio-

Continued on page 64.

material development studies need to consider the interactions of materials with *in vivo* proteins, as well as with bacterial pathogens.

Conclusions

As a crucial step leading to infection development, the creation of new tools to experimentally measure and model bacterial adhesion can lead to health benefits. In particular, we discussed how atomic force microscopy and thermodynamic modeling could be used to study the fundamental adhesion processes related to urinary tract infections and bacterial infections on biomaterials.

References

1. Van Loo, J. and Jonkers, N., "Evaluation in Human Volunteers of the Potential Anticarcinogenic Activities of Novel Nutritional Concepts: Prebiotics, Probiotics and Synbiotics," *Nutrition, Metabolism, and Cardiovascular Diseases,* Vol. 11, No. 4, 2001, pp. 87-93.
2. WHO Report in World Health Organization Report on Infectious Diseases, World Health Organization, Geneva, Switzerland, 1999.
3. Klevens, R.M., Morrison Melissa, A., and Nadle, J., *et al.*, "Invasive Methicillin-Resistant *Staphylococcus aureus* Infections in the United States," *The Journal of the American Medical Association,* Vol. 298, No. 15, 2007, pp. 1763-71.
4. Jass, J., Schedin, S., Fallman, E., *et al.*, "Physical Properties of *Escherichia coli* P pili Measured by Optical Tweezers," *Biophysical Journal,* Vol. 87, No. 6, 2004, pp. 4271-83.
5. Abu-Lail, L.I., Liu, Y., Atabek, A., and Camesano, T.A., "Quantifying the Adhesion and Interaction Forces Between *Pseudomonas aeruginosa* and Natural Organic Matter," *Environmental Science and Technology,* Vol. 41, No. 23, 2007, pp. 8031-8037.
6. Liu, Y., Gallardo-Moreno, A.M. and Camesano, T.A. Abstracts of Papers, 106 ASM General Meeting, Orlando, Florida, United States, 20-24 May 2006.
7. Emerson, R.J., IV, Bergstrom, T.S., Liu, Y., et al., "Microscale Correlation between Surface Chemistry, Texture, and the Adhesive Strength of *Staphylococcus epidermidis*," *Langmuir,* Vol. 22, No. 26, 2006, pp. 11311-11321.
8. Camesano, T.A., Liu, Y., and Datta, M., "Measuring Bacterial Adhesion at Environmental Interfaces with Single-Cell and Single-Molecule Techniques," *Advances in Water Resources,* Vol. 30, No. 6-7, 2007, pp. 1470-1491.
9. Camesano, T.A., Liu, Y., and Gallardo-Moreno, A., (Worcester Polytechnic Institute, USA), PCT International Patent Application, pp. 47, WO 2007109689, 2007.
10. Van Oss, C. J., Interfacial Forces in Aqueous Media. Dekker, New York, New York, 1994
11. Liu, Y., Strauss, J., and Camesano, T.A., "Thermodynamic Investigation of *Staphylococcus epidermidis* Interactions with Protein-Coated Substrata," *Langmuir,* Vol. 23, No. 13, 2007, pp. 7134-7142.
12. Sobel, J.D., "Bacterial Etiologic Agents in the Pathogenesis of Urinary Tract Infection," *The Medical Clinics of North America,* Vol. 75, No. 2, 1991, pp. 253-273.
13. Foxman, B., Barlow, R., D'Arcy, *et al.*, "Urinary Tract Infection: Self-Reported Incidence and Associated Costs," *Annals of Epidemiology,* Vol. 10, No. 8, 2000, pp. 509-515.
14. Reid, G., "Applications from Bacterial Adhesion and Biofilm Studies in Relation to Urogenital Tissues and Biomaterials: A Review," *Journal of Industrial Microbiology,* Vol. 13, No. 2, 1994, pp. 90-96.
15. Foxman, B., "Epidemiology of Urinary Tract Infections: Incidence, Morbidity, and Economic Costs," *The American Journal of Medicine,* Vol. 113, Suppl. 1A, 2002, pp. 5S-13S.
16. Russo Thomas, A. and Johnson James, R., "Medical and Economic Impact of Extraintestinal Infections due to *Escherichia coli*: Focus on an Increasingly Important Endemic Problem," *Microbes and Infection / Institute Pasteur,* Vol. 5, No. 5, 2003, pp. 449-56.
17. Blondeau, J.M., "Current Issues in the Management of Urinary Tract Infections: Extended-Release ciprofloxacin as a Novel Treatment Option," *Drugs,* Vol. 64, No. 6, 2004, pp. 611-628.
18. Blatherwick, N.R. and Long, M.L., "Studies of Urinary Acidity. II. The Increased Acidity Produced by Eating Prunes and Cranberries," *Journal of Biological Chemistry,* Vol. 57, 1923, pp. 815-818.
19. Blatherwick, N.R., "The Specific Role of Foods in Relation to the Composition of the Urine," *Archives of Internal Medicine,* Vol. 14, 1914, pp. 409-450.
20. Bodel, P.T., Cotran, R., and Kass, E.H., "Cranberry Juice and the Antibacterial Action of Hippuric Acid," *Journal of Laboratory and Clinical Medicine,* Vol. 54, 1959, pp. 881-888.
21. Walsh, B.A., "Urostomy and Urinary pH," *Journal of ET nursing,* Vol. 19, No. 4, 1992, pp. 110-113.
22. Sobota, A.E., "Inhibition of Bacterial Adherence by Cranberry Juice: Potential Use for the Treatment of Urinary Tract Infections," *The Journal of Urology,* Vol. 131, No. 5, 1984, pp. 1013-1016.
23. Pinzon-Arango, P.A., Liu, Y., and Camesano, T.A., (2007) Abstracts of Papers, 234th ACS National Meeting, Boston, Massachusetts, United States, 19-23 August 2007.
24. Liu, Y., Black, M.A., Caron, L., and Camesano, T.A., "Role of Cranberry Juice on Molecular-scale Surface Characteristics and Adhesion Behavior of *Escherichia coli*," *Biotechnology and Bioengineering,* Vol. 93, No. 2, 2006, pp. 297-305.
25. Camesano, T.A., Liu, Y., and Pinzon-Arango, P.A., "Cranberry Prevents the Adhesion of Bacteria: Overview of Relevant Health Benefits," *AgroFOOD Industry Hi-Tech,* Vol. 18, No. 1, 2007, pp. 24-27.
26. Liu, Y., Gallardo-Moreno, A.M., and Camesano, T.A., (2006) Abstracts of Papers, 232nd ACS National Meeting, San Francisco, California, United States, 10-14 September 2006.
27. Shahidi, F., Weerasinghe, D.K., and Editors, ACS Symposium Book: Nutraceutical Beverages: Chemistry, Nutrition, and Health Effects, American Chemical Society, Washington, DC, 2004.
28. Howell, A.B., "Cranberry Proanthocyanidins and the Maintenance of Urinary Tract Health," *Critical Reviews in Food*

Science and Nutrition, Vol. 42, No. 2 Suppl., 2002, pp. 273-278.
29. Howell, A.B.V., Nicholi, (2003), "Plant Proanthocyanidin Extract Effective at Inhibiting Adherence of Bacteria with P-type Fimbriae to Surfaces," U.S. Patent 6608102, 2003, pp. 24.
30. Howell, A.B., Reed, J.D., Krueger, C.G., *et al*., "A-type Cranberry Proanthocyanidins and Uropathogenic Bacterial Anti-Adhesion Activity," *Phytochemistry*, Vol. 66, No. 18, 2005, pp. 2281-2291.
31. Howell, A.B., "Bioactive Compounds in Cranberries and their Role in Prevention of Urinary Tract Infections," *Molecular Nutrition and Food Research*, Vol. 51, No. 6, 2007, pp. 732-737.
32. Zafriri, D., Ofek, I., and Adar, R., *et al*., "Inhibitory Activity of Cranberry Juice on Adherence of Type 1 and Type P Fimbriated *Escherichia coli* to Eucaryotic Cells," *Antimicrobial Agents and Chemotherapy*, Vol. 33, No. 1, 1989, pp. 92-98.
33. Steinberg, D., Feldman, M., Ofek, I., and Weiss, E.I., "Effect of a High-Molecular-Weight Component of Cranberry on Constituents of Dental Biofilm," *Journal of Antimicrobial Chemotherapy*, Vol. 54, No. 1, 2004, pp. 86-89.
34. Burger, O., Ofek, I., and Tabak, M., et al., "A High Molecular Mass Constituent of Cranberry Juice Inhibits Helicobacter Pylori Adhesion to Human Gastric Mucus," *FEMS Immunology and Medical Microbiology*, Vol. 29, No. 4, 2000, pp. 295-301.
35. Darouiche, R.O., "Treatment of Infections Associated with Surgical Implants," *New England Journal of Medicine*, Vol. 350, No. 14, 2004, pp. 1422-1429.
36. Hetrick, E.M. and Schoenfisch, M.H., "Reducing Implant-Related Infections: Active Release Strategies," *Chemical Society Reviews*, Vol. 35, No. 9, pp. 780-789.
37. Correa, L. and Pittet, D., "Problems and Solutions in Hospital-Acquired Bacteraemia," *The Journal of Hospital Infection*, Vol. 46, No. 2, 2000, pp. 89-95.
38. Raad, I., "Intravascular-Catheter-Related Infections," *Lancet*, Vol. 351, No. 9106, 1998, pp. 893-8.
39. Kloos, W., **Taxonomy and Systematics of *Staphylococci* Indigenous to Humans,** Churchill Livingstone, New York, 1997.
40. Noble, W., ***Staphylococcal* Carriage and Skin and Soft Tissue Infection,** Churchill Livingstone, New York, 1997.
41. Mack, D., "Molecular Mechanisms of *Staphylococcus epidermidis* Biofilm Formation," *The Journal of Hospital Infection*, Vol. 43, 1999, pp. S113-S125.
42. Blot Stijn, I., Depuydt, P., and Annemans, L., *et al*., "Clinical and Economic Outcomes in Critically Ill Patients with Nosocomial Catheter-related Bloodstream Infections," *Clinical Infectious Diseases*, Vol. 41, No. 11, 2005, pp. 1591-1598.
43. Francolini, I., Donelli, G., and Stoodley, P., "Polymer Designs to Control Biofilm Growth on Medical Devices," *Reviews in Environmental Science and Bio/Technology*, Vol. 2, No. 2-4, 2004, pp. 307-319.
44. Gristina, A.G., "Biomaterial-centered Infection: Microbial Adhesion versus Tissue Integration," *Science*, Vol. 237, No. 4822, 1987, pp. 1588-1595.
45. Sherertz, R.J., Forman, D.M., and Solomon, D.D., "Efficacy of Dicloxacillin-coated Polyurethane Catheters in Preventing Subcutaneous Staphylococcus Aureus Infection in Mice," *Antimicrobial Agents and Chemotherapy*, Vol. 33, No. 8, 1989, pp. 1174-1178.
46. Stigter, M., Bezemer, J., de Groot, K., and Layrolle, P., "Incorporation of Different Antibiotics into Carbonated Hydroxyapatite Coatings on Titanium Implants, Release and Antibiotic Efficacy," *Journal of Controlled Release*, Vol. 99, No. 1, 2004, pp. 127-137.
47. Price, J.S., Tencer, A.F., Arm, D.M., and Bohach, G.A., "Controlled Release of Antibiotics from Coated Orthopedic Implants," *Journal of Biomedical Materials Research*, Vol. 30, No. 3, 1996, pp. 281-286.
48. Ista, L.K., Fan, H.Y., Baca, O., and Lopez, G.P., "Attachment of Bacteria to Model Solid Surfaces: Oligo (Ethylene Glycol) Surfaces Inhibit Bacterial Attachment," *Fems Microbiology Letters*, Vol. 142, No. 1, 1996, pp. 59-63.
49. Chapman, R.G., Ostuni, E., and Liang, M.N., et al., "Polymeric Thin Films that Resist the Adsorption of Proteins and the Adhesion of Bacteria," *Langmuir*, Vol. 17, No. 4, 2001, pp. 1225-1233.
50. Lee, S. and Voeroes, J., "An Aqueous-Based Surface Modification of Poly (dimethylsiloxane) with Poly (ethylene glycol) to Prevent Biofouling," *Langmuir*, Vol. 21, No.

Concludes on page 66.

25, 2005, pp. 11957-11962.
51. Bologna, R.A., Tu, L.M., and Polansky, M., *et al.*, "Hydrogel/Silver ion-coated Urinary Catheter Reduces Nosocomial Urinary Tract Infection Rates in Intensive Care Unit Patients: A Multicenter Study," *Urology*, Vol. 54, No. 6, 1999, pp. 982-987.
52. Camesano, T.A. and Mello, C., ACS Symposium Book: Structure, Interactions and Reactivity at Microbial Surfaces, American Chemical Society, Washington, DC, 2008.
53. Liu, Y., Strauss, J., and Camesano, T.A., "Adhesion forces between *Staphylococcus epidermidis* and surfaces bearing self-assembled menolayers in the presence of model proteins," *Biomaterials*, Vol. 29, No. 33, 2008, pp. 4374-4382.

Acknowledgements

This work was supported in part by the National Science Foundation (BES 0238627 and EEC 0452809). Paola Pinzon-Arango received Fellowship support from the American Association for University Women.

We also thank Dr. Amparo Gallardo-Moreno, Dr. Stephen Heard, Dr. W. Grant McGimpsey, Dr. Ray Emerson, Ms. Arzu Atabek, Ms. Laila Abu-Lail, and Mr. Eftim Milkani for the help and discussions throughout the course of these studies, and Ms. Xiaoshu Dai and Professor Satya Shivkumar for their assistance with SEM measurements.

About the Authors

Yatao Liu earned his BS and MS in chemical engineering from East China University of Science and Technology, Shanghai, China in 2003. He is currently pursuing his PhD in chemical engineering at Worcester Polytechnic Institute, Massachusetts. His research involves unveiling the mechanisms of cranberries preventing urinary tract infections. He also is engaged in developing new implanted medical materials to prevent infections based on the in-depth understanding of bacterial adhesion. He received the American Institute of Chemists Award in 2007 and is the recipient of George I. Alden Fellowship. He has published more than 10 peer-reviewed research articles and holds two granted patents and two pending patents. He can be contacted by email: yataoliu@gmail.com.

Paola Pinzon-Arango graduated with a BS in chemical engineering from Worcester Polytechnic Institute (WPI) in Worcester, Massachusetts in 2005, where she conducted research on understanding the effects of cranberry juice on bacterial adhesion to bladder cells. During her undergraduate studies, she also worked with the Ecole Nationale Supérieure des Industries Chimiques, in Nancy, France, where she investigated the stabilization of oil-in-water emulsions to encapsulate lidocaine for a controlled release drug delivery system. She received her MS in biomedical engineering from WPI in 2008. Pinzon-Arango has been engaged in research aimed at understanding the mechanisms by which cranberry juice and its isolated compounds inhibit the adhesion of *E. coli* to uroepithelial cells and how cranberry modifies surface properties of bacteria. She was awarded a Selected Professions Fellowship from the American Association of University Women in 2006. She is currently a PhD candidate from the Department of Chemical Engineering at WPI. Her research interests include scanning probe microscopy, bacterial adhesion, and effects of material coatings on *in vivo* implant performance. She can be contacted by email: ppinzon@wpi.edu.

Joshua Strauss is among the first researchers to occupy Worcester Polytechnic Institute's new research facility, Life Sciences and Bioengineering Center at Gateway Park. His research encompasses the use of antimicrobial cecropins as a means to detect and eradicate pathogenic *E. coli* from food supplies. A graduate of WPI's chemical engineering program in February 2007, he is pursuing his Masters under the direction of Professor Camesano. His laboratory specializes in using equipment such as the atomic force microscope and the quartz crystal microbalance with dissipation monitoring. His work has been published in Langmuir and in two symposium book chapters with the American Chemical Society. In addition, he has presented several posters at meetings, including the American Chemical Society, the American Society for Microbiology, and the Materials Research Society. He can be contacted by email: josh1@wpi.edu.

Terri A. Camesano heads a research group in bacterial adhesion and interaction forces at Worcester Polytechnic Institute (WPI), in Worcester, Massachusetts. She received a PhD from the Pennsylvania State University in environmental engineering, an MS in environmental engineering from the University of Arizona, and a BS in chemical engineering and environmental science from the University of Rochester. She has been employed at WPI since 2000 and was named Associate Professor of Chemical Engineering in 2006. Camesano's research focuses on understanding bacterial adhesion, the initial event in biofilm formation. This work has relevance to a number of biomedical and environmental problems, such as microbial colonization of catheters and biomaterials, subsurface bioremediation, prevention of pathogenic microorganisms in drinking water, and the interactions between bacteria and host tissue in the body. Camesano is the author or co-author of more than 30 journal publications and is the recipient of an NSF CAREER Award (2003) and the Sigma Xi Junior Faculty Award for Outstanding Research (2005). She can be contacted by email: terric@wpi.edu.

Worcester Polytechnic Institute, Department of Chemical Engineering, Life Sciences and Bioengineering Center at Gateway Park, 100 Institute Rd., Worcester, Massachusetts 01609, USA.

This article is being reprinted with permission from the October 2008 issue of Regulatory Focus, the monthly publication of the Regulatory Affairs Professional Society (RAPS).

For more information about RAPS and *Focus*, visit www.raps.org.

Considering Outsourcing? Risks and Benefits for FDA-Regulated Firms

by Mukesh Kumar, PhD, RAC

From its modest start about 30 years ago as an alternative to academic institutions for laboratory and clinical work, outsourcing has grown into a $16 billion industry in the US alone. It spans all aspects of drug development, from discovery to clinical development to product approval, and even included commercialization and postmarketing support. With more than 90% of the biopharmaceutical industry comprised of small businesses with limited resources,[1] many firms outsource product development to either reduce expenses or compensate for lack of core competencies. Contract Research Organizations (CROs) offer an excellent outsourced resource to guide firms through the risky, costly, and time-consuming myriad of drug development pathways.

The cost of drug development has risen steadily over the last two decades, partly as the result of increased operational expenses, but mostly due to the need for increased knowledge of complex biological processes and the capability to monitor and understand safety-related aspects of drugs. The last decade also has seen high-profile cases where approved drugs were withdrawn due to unexpected safety issues not identified during development phases and promising therapies that failed at late stages of development. These have led the US Food and Drug Administration (FDA) to require increasing amounts of data to support new drug applications. Coupled with the drying up of product pipelines and loss of revenue due to several blockbuster drugs going off patent within a short span of time, this FDA requirement has exacerbated financial and operational problems for biopharmaceutical companies, both large and small. Changing industry dynamics have led to extensive, across-the-board cost-cutting measures.

But companies must innovate to survive. While they are striving to control costs, they also need to increase spending on R&D to create profitable new proprietary products. CROs offer a solution to this dilemma: they can develop drugs faster than pharmaceutical companies with comparable quality and lower overall cost. Large companies such as GlaxoSmithKline, Pfizer, and Wyeth have unveiled strategic shifts in new product development policies, relying increasingly on CROs for R&D and subsequent development.[2,3]

CROs are uniquely capable of addressing these issues because of their diverse product experiences (even within the same indications), infrastructural capabilities and high concentration of human resources. Approximately 500 CROs compete around the world.[4] Large CROs offer a wider range of services while smaller ones specialize in specific areas, from strategic consultancy to clinical or preclinical services. While large pharmaceutical companies still account for about 70% of the total revenue for the outsourcing industry, the share of the smaller companies is steadily increasing and is expected to continue growing over the next few years. Also, due to the globalization of drug development, there is a trend toward increasing revenue from outside the US. Currently, about 40% of CROs' revenues are generated outside the US and that figure is expected to rise to more than 60% by 2010. The CRO industry is growing at an annual rate of 12.6% and is expected to reach about $30 billion by 2011, with one of the highest earning rates per employee in any industry.[4]

Almost all biopharmaceutical companies need to consider outsourcing all or parts of their operations to CROs. The CRO industry has evolved from the tactical or transactional outsourcing model to the role of a strategic partner. And as in any partnership, the biopharmaceutical company needs to consider

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2009,
Vol. 29 No. 1

several factors before deciding which CRO to work with. Among these are potential supply chains and markets, the risks and benefits of outsourcing operations to particular contractors (whether down the street or overseas), alternatives to outsourcing, and how to maintain an effective relationship with contractors and suppliers in producing safe, effective and compliant products for the marketplace. The main issues companies should consider before outsourcing are discussed below.

Harnessing Technology Assets: Building Core Competencies

CROs offer ready availability of core competencies that may be hard for the biopharmaceutical company to develop internally in a cost- and time-effective manner, but outsourcing could be considered as stunting the development of internal capabilities for conducting strategically important research at a later time. This is of particular concern for small and medium-size enterprises that look at working with more-experienced and technically advanced CROs as a means of training their personnel for future projects. Companies need to identify potential areas for building internal core competencies early on. Most small and medium-sized biopharmaceutical companies focus their core efforts on discovery, strategic planning and conducting smaller clinical trials locally; however, certain areas – such as animal testing and conducting research in countries where the biopharmaceutical company has little or no native expertise – are better left to the CROs. By targeting the areas for building core competency, a biopharmaceutical company can collaborate with the CRO to train its people on the job. This hands-on training must be complemented by training and education programs available in the public domain because interaction with the CRO cannot replace education.

Long-Term Interests

Companies with one or a few products rely heavily upon positive relationships with a few opinion leaders. These could be the individuals who discover the technology they are developing, or key investigators and consultants. Hence, developing long-term relationships with these individuals and organizations is critical for the company's survival. CROs might not be aware of the strategic importance of a particular investigator or site to the company. Since the CRO's job is to assure timely and high-quality project execution, they might get into a negative relationship with the key investigator on compliance-related issues. To avoid that, the CRO must be made aware of the logistical role of key investigators. Training and mentoring programs for key investigators can be built into the project to ensure higher compliance. This is particularly important for global trials where each country in which trial sites are located might have local high-profile investigators who are critical to the current project's completion and future company plans.

Concludes on page 70.

"Outsourcing is commonly misunderstood as unidirectional flow of contract work from the developed countries to emerging regions in Asia and Latin America."

Risk Mitigation

A key component of the decision to outsource usually is the desire to reduce the risk of failure in developing desired products. Companies seek strategic advice from the CRO about the best regulatory pathways, preclinical and clinical studies, safety monitoring and marketing research. A good consultant can help a company avoid costly mistakes, identify issues before they become concerns, and help develop contingency plans in case things do not happen as predicted. Companies tend to hire strategic consultants with whom senior managers feel comfortable sharing confidential information. Additional factors to consider are the CRO's operational experience: specifically, depth and width of expertise, technological advancement and global reach.

Strategic Partnership

The outsourcing industry has a come a long way from being used primarily for transactional or tactical services for specific tasks in the 1980s and 1990s, to serving as strategic partners participating in all aspects of drug development. As a result of their increased experience and technical capabilities, most CROs feel comfortable sharing development risks with their clients by working for equity or using deferred compensation models. CROs have developed highly skilled global teams that provide valuable global reach, not only for development steps but also access to new markets.

Discovery, which traditionally resided with the innovator company, is the latest activity to be added to the list of outsourced functions. The top biopharmaceutical companies lead in this new strategic shift in policy, where dedicated facilities are created by partners catering to the new molecule discovery needs of the client firm.

Most of the world's top pharmaceutical corporations have started reducing their in-house R&D budgets and increasing outsourcing to new regions of the world such as Asia – primarily India, China, and Singapore – and Latin America.[3] Small biopharmaceutical companies, similarly, can tap into this resource by outsourcing early-stage development steps to CRO partners, while concentrating their limited resources on high-end product management. There is a trend toward companies concentrating on senior management while outsourcing practically the entire development process to CROs. Of course, such extensive outsourcing poses an increased risk to small companies because of intellectual property concerns for mutually developed technologies, particularly when combined with strategic partnership agreements and equity or deferred compensation contracts. Such partnerships need extensive trust-building efforts and good legal contracts.

Conclusion

Outsourcing is commonly misunderstood as unidirectional flow of contract work from the developed countries to emerging regions in Asia and Latin America. However, the bulk of pharmaceutical contract research is done by CROs headquartered in the US and Europe. Rising operating costs worldwide, particularly in China and India, have led some analysts to predict a slowing of outsourcing to these areas, and even reversal of activities to the West. For biopharmaceutical firms, the need for strategic outsourcing and international localization of development steps cannot be emphasized enough. The place to start in developing an overall outsourcing strategy is with an honest appraisal of the contribution of all parties, including developers and the CROs, to the drug development value chain. The four keys to an effective outsourcing strategy are:

- identifying the appropriate tasks to outsource
- developing a rationale and process for CRO selection
- committing to managing CROs
- periodically reviewing deliverables

It is well accepted that outsourcing offers key advantages to biopharmaceutical companies of all sizes. However, for small and medium-size business, it could define the difference between being profitable and going out of business.

References

1. "FDA Final Rule Human Subject Protection." *Federal Register* Vol. 73, No. 82, 28 April 2008.
2. www.in-pharmatechnologist.com/Industry-Drivers/GSK-continues-shift-in-strategic-direction.
3. www.outsourcing-pharma.com/Preclinical-Research/GVK-BIO-secures-Wyeth-deal.
4. Hoang, T., et al. "Contract Research Helps Keep Drug Pipelines Flowing Sector Focus Report," Turner Capital Investment, Berwyn, Pennsylvania, July 2008. www.turnerinvestments.com/index.cfm/fuseaction/commentary.detail/ID/2661/CSID/387/.

About the Author

Mukesh Kumar, PhD, RAC is a senior director, regulatory affairs, at Amarex Clinical Research LLC, located in Germantown, Maryland, which is a full-service CRO offering strategic planning, trial management, data management, and statistical analysis services for global clinical trials. Kumar is a member of the Regulatory Affairs Professionals Society's Board of Editors for *Regulatory Focus*. He can be reached by email: mukeshk@amarexcro.com.

Supplement to

PHARMACEUTICAL ENGINEERING

Country Profile

A look at the Pharmaceutical Industry in

CHINA

Produced in collaboration with ISPE China

www.ISPE.org

ENGINEERING PHARMACEUTICAL INNOVATION

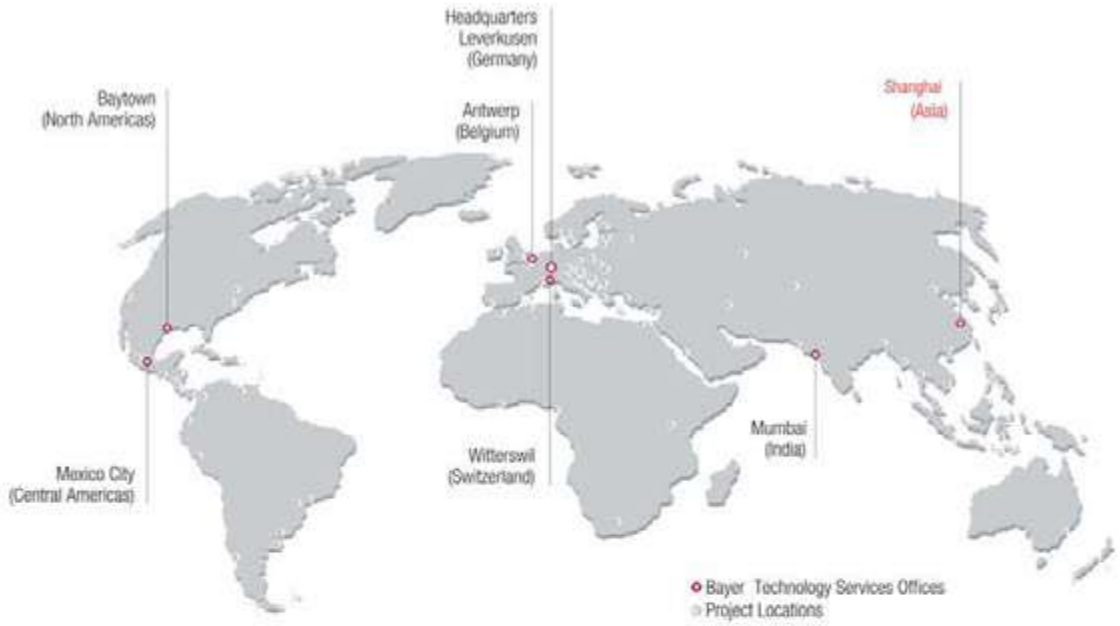
ISPE

Bayer Technology Services

INNOVATION **ENGINEERING** **OPTIMIZATION**

Global Expertise & Local Experience for Pharmaceutical Industry in China

API Formulation Biotech



Innovation

Technology and Process Expertise
- High Sensitivity Protein Array
- Simulated Moving Bed Chromotography
- Modular MicroReaction Technology
- UVivatec- System for Virus Inactivation

... ...

Engineering

From Feasibility Study to Validation
- Site Master Planning
- Design & Execution
- Qualification & Validation
- GMP Consultancy

... ...

Optimization

Solutions for Operational Excellence
- Advanced Process Control (incl. MES)
- PAT
- Supply Chain Management

... ...

Bayer Technology & Engineering (Shanghai) Company Limited
No. 82 Muhua Rd. Shanghai Chemical Industry Park 201507 T: 8621-61465100 F: 8621-67120393 E: btsasia@bayertechnology.com

Our Reputation is Building

Feasibility and Masterplan

Project Management

EPCM / Total Solutions

Project Controls

Validation

Controlled Environment Specialists:

Pharmaceutical

Research & Development

Laboratories

Food & Beverage

Electronics

Hooker Cockram, an International Company that offers a range of specialist skills and proven expertise in the areas of Project Management, Design Management, Construction Management, Building Contracting Services and Project Controls.

A heritage of over 146 years is augmented by our commitment to excellence and achieving the highest professional standards through innovation and application of proven methods and techniques.

"Hooker Cockram have operated in China for the past 15 years with established offices in Shanghai, Tianjin and Suzhou. During that time we have delivered numerous facilities for a range of International clients all over China. The majority of these projects were Clean Environment facilities including several sterile facilities for the worlds leading pharmaceutical companies. We have a high degree of quality control in the design and construction of these challenging projects and offer International Quality at competitive prices…… "

Greg Mithen, HC General Manager (China)

AUSTRALIA . CHINA . INDIA . PUERTO RICO . USA
澳大利亚 . 中国 . 印度 . 波多黎各 . 美国
www.hookercockram.com CHINA: +86 21 5238 3666 USA: +1 610 977 2010 AUST: +61 3 8862 8888

HOOKER COCKRAM

ENGINEERING PHARMACEUTICAL INNOVATION

Dear ISPE Members,

On behalf of the ISPE China Office and the ISPE Greater China Steering Committee, we would like to present you with this Country Profile of Greater China, which contains comprehensive information about the pharmaceutical industry in China mainland, Hong Kong SAR, Macau SAR, and Taiwan.

China, one of the countries in the world experiencing double digit growth, has successfully attracted many investors from different industries around the world. China has recently successfully organized the Olympic games, which showcased China to the world and vice versa. Shanghai will host another world class large scale event in 2010 – the World Expo.

With a history of Traditional Chinese Medicine (TCM) application for thousands of years and a wide-range application of chemical drugs and biotech products today, Greater China plays a key role in the global pharmaceutical industry. A dramatic trend in this industry is that more and more operations, including R&D, are moving to China. Considering the importance of this market, ISPE set up its China office in Shanghai at the beginning of 2008 to better serve local members. Tightly cooperating with the China Center of Pharmaceutical International Exchange (CCPIE) under the State Food and Drug Administration (SFDA), more than 30 volunteer leaders have formed the ISPE Greater China Steering Committee and are driving ISPE activities fervently here. Special thanks to all volunteer leaders who were involved in contributing information for this China Country Profile.

We hope this Country Profile will offer you some insights about the importance of the pharmaceutical industry in Greater China and we look forward to seeing you here!

Yours sincerely,

Jason Tang
Chairman, ISPE Greater China Steering Committee

Hang Song
Co-Chairman, ISPE Greater China Steering Committee

Cheryl Siow
Manager, ISPE China Office

Table of Contents

History of the Pharmaceutical Industry in China 5
Strengths and Challenges Facing the Industry 6
Geographical Breakdown by Regions 7
Size and Growth of the Industry 8
Market Size Breakdown by City Tier 9
Academic Affiliations 9
Regulatory Agencies in Greater China 10
A Brief Introduction to the ISPE China Affiliate 13
Pharmaceutical Associations and Organizations in China 15
References 15
Acknowledgements 15

For more information, please visit the ISPE China Web site at www.ISPE.org.cn or contact:

ISPE China Office
Suite 2302, Wise Logic International Center,
No.66 North Shanxi Road,
Shanghai 200041 China
Tel: +86 21-5116 0265
Fax: +86 21-5116 0260
Email: china@ispe.org

History of the Pharmaceutical Industry in China

The history of the pharmaceutical industry in China can be traced back to thousands of years ago. The ancient Chinese started to use some specific species of herbs as medicines and developed a systemic Chinese medicine theory. The most popular form of Traditional Chinese Medicine is water extract with a mix of different kinds of medicinal herbs – still under use today. The prescriptions (kinds and dosages of the medicinal herbs) of the water extract form vary from patient to patient and from time to time even for the same patient. Thus, the water extract form is a very customized and individualized pharmaceutical product. However, albeit this form may be the most precise way to treat some patient's specific disease, it is inconvenient for patients to bring it with them and it takes time for people to cook before taking the extract – too late for emergencies. Later on, Chinese pharmacists developed some traditional dosage forms, such as the honey pill, fine powder, concentrated syrup, quick-release small pill, etc. Each drug with these traditional dosage forms has a fixed prescription, manufacturing process, and indication – same as today's Chinese or western drugs.

In the 1800s, western drugs entered China mainland. Penicillin was one of the most important drugs during that period as it saved many lives in China. There were quite some conflicts between western medicines and Chinese medicines from time to time as the two theories are totally different from the very basis. After many years of debate, today we are beginning to see 'harmonization' between them – at least both are quite popularly used and, there is some integration between them in some fields.

Also, the introduction of western drugs influenced the development of Chinese drugs to some extent. That's why today we can see a lot of Chinese drugs with the same dosage forms as western drugs like injectable, capsule, tablet, etc.

In the past 30 years, the Chinese pharmaceutical industry has been developing very fast. A lot of MNCs entered China, and most of them are quite successful with aggressive expansion. Domestic companies also grew up. And a lot of mergers among pharmaceutical companies happened especially in the past 15 years.

At present, China mainland can produce 1,500 types of drug substances, many of which lead the world in terms of output, including penicillin and vitamin C. A number of botanic and natural drugs, such as anti-infective berberine and anti-tumor colchicine have been mass-produced and widely used in China. China's antibiotic, vitamin, hormone, antipyretic and analgesic, amino acid, and alkaloid products make up considerable shares of the international pharmaceutical market. China's artemisinin products are used all over the world, significantly contributing to the international anti-malaria efforts. Today, China can produce more than one billion doses a year of 41 types of vaccines against infection caused by 26 kinds of viruses and pathogenic bacteria. Among them, the country's annual output of vaccines for preventing common infectious diseases such as hepatitis B, poliomyelitis (infantile paralysis), measles, pertussis, diphtheria, and tetanus, can serve 500 million people. In addition to meeting the domestic demand, China also provides vaccines to the World Health Organization (WHO) for disease prevention in other countries. China produces more than 3,000 types of medical devices, among which high-tech diagnosis and treatment products such as the digital X-ray, magnetic resonance, ultrasonic and computed tomography apparatus hold considerable market shares. By the end of 2007, China had 12,591 enterprises producing medical devices, and 6,913 pharmaceutical enterprises (including producers of Chinese medicinal drink chips and oxygen for medical use), of which 4,682 were producers of active pharmaceutical ingredients and preparations.[1]

Major Focus of the Industry

- Chemical API
- Western formulations
- Biotech
- TCM (finished products and Chinese medicinal drink chips)
- Medical devices and hygienic materials
- Veterinary drugs

Strengths and Challenges Facing the Industry

China, in terms of both its healthcare system and pharmaceutical market poses both promises and challenges. As the world's most populous country, and one in possession of the fastest growing major economy in the world, the nation offers a vast array of opportunities.

The past two decades has brought significant changes to the pharmaceutical industry in China, from the arrival of foreign companies and multinationals to the expansion and development of the domestic production capabilities. This has and will continue to bring many changes and challenges to the marketplace.

Regulatory

The responsibility for regulating drugs has undergone a lot of changes in the past decade in China. Originally part of the domain of the Ministry of Health until 1998, the State Drug Administration (SDA) was formed as a separate bureau in 1999. This Agency's name was changed in 2003 to the State Food and Drug Administration (SFDA) and remained separate. In July 2007, irregularities within the organization called China's drug manufacturing practices into question. In March of this year, the SFDA was amalgamated back into the Ministry of Health.

The shift in regulatory requirements has proved swift in a country undergoing such a fast paced development. There will no longer be the distinction of products for the domestic market being treated differently as products for export or import. Foreign companies brought with them expertise in many fields. This knowledge has been taken onboard by local employees and manufacturers quickly, and many local manufacturers seek help from abroad to achieve their desired goals.

The SFDA are currently producing a new set of GMP guidelines that will be more robust and reflect other international standards. There will be many companies facing changes to manufacturing procedures in order to meet these requirements.

The new GMPs will have far reaching consequences on facility design, equipment selection and qualification, operating procedures, laboratories and testing, warehousing, and logistics; and could very well be a daunting prospect for many small companies with a limited product portfolio.

Previous inspections would have been passed and the products reputation for safety and quality attributes never called into question. How the regulatory bodies steer this change and enhancement of the production facilities over a suitable time period is paramount.

Research and Development – Pricing and the Pipeline Problem

There can be no factor of greater importance than the launch of new therapies to the pharmaceutical industry. As such, all innovator companies are reliant on novel drugs not only to increase market share, but also to secure their market position. This has never been more evident than at the present time as many large companies are facing patent expirations on "blockbuster" products. This pressure is compounded by the increasing number and sophistication of generics manufacturers.

As a result, effective and successful Research and Development (R&D) programs are essential for these well established companies. The cost of bringing a drug to the market place runs into the hundreds of millions of dollars. So, any way to reduce this cost is highly attractive to the manufacturer.

Pharmaceutical R&D in China has not on the whole been the domain of individual companies, but more widely academically driven and government funded.

This is ultimately biased in the favor of research rather than that of development, resulting in a demographic comprised of many extremely talented, but under utilized research scientists. This and the relatively low cost of building and operation has already attracted a number of international pharmaceutical companies to open R&D facilities in China.

Pharmaceutical manufacturers also attribute the cost of clinical trials as one of the largest barriers to drug innovation. By performing clinical trials in China for submission to foreign drug administrations, it also may be possible to cut costs. However, there are two major challenges in conducting clinical trials in China, including that China has one of the longest application review times in the world and that the SFDA needs to approve the application first before it goes to an ethics committee.

Traditional/ Herbal Medicines

The FDA has formally acknowledged Traditional Chinese Medicine (TCM) and its therapeutic qualities.

There are currently TCMs that have passed successful clinical trials that are awaiting FDA ruling. Further patents for TCMs have been sold to the US, Europe, Japan, Korea, and Australia, which are awaiting pilot production and trials. However, TCMs are a cause of confusion and concern in the foreign market place.

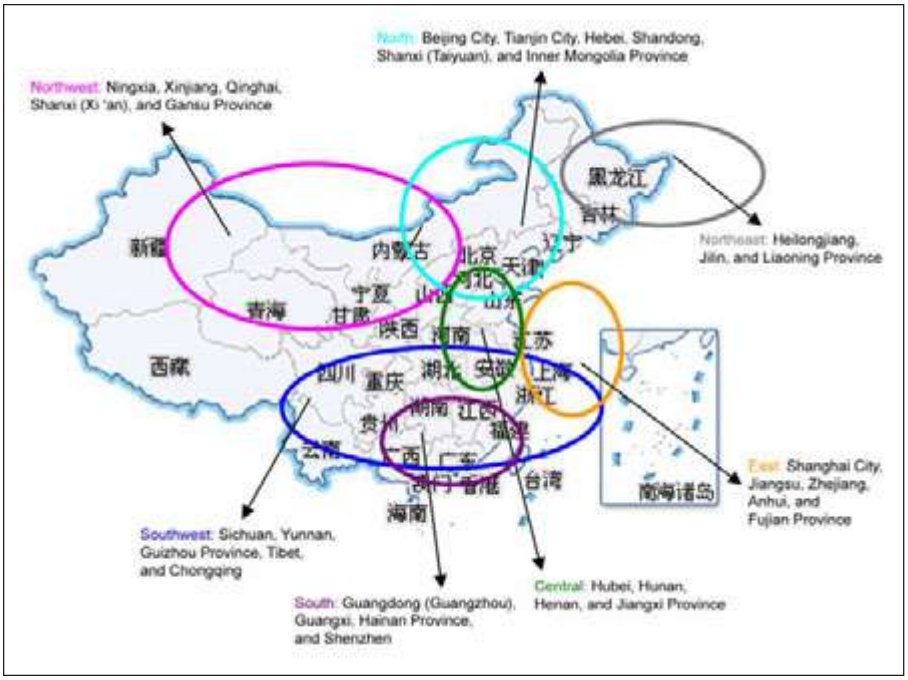
One major factor is that China affords TCMs a protected status which is not afforded in other countries. In the US and Europe, drugs have to follow the western allopathic drug registration process, so ingredients not in the European or North American Pharmacopoeia require a new drug registration.

Not only are ingredients an issue, but so is the production process. In Europe, Annex 7 of the EU GMP addresses the production of herbal medicines. But the situation in China has long seemed far from clear as to which type of product would fall under the GMP regulations and thus, the scrutiny of the SFDA.

Concludes on page 8.

Geographical Breakdown by Regions

Greater China includes China mainland, Hong Kong SAR, Macau SAR, and Taiwan. China mainland consists of 27 provinces/autonomous regions and four big cities under direct jurisdiction of a central government.



The breakdown for Greater China by geographical regions is below:

No	Region	Description
1	Eastern China	Eastern China consists of Shanghai City, Jiangsu, Zhejiang, Anhui, and Fujian provinces. The Yangtze River Delta, which also may be called Changjiang Delta, is located in this region. Many of MNCs have subsidiaries here, including operations for manufacturing, S&M, and R&D, etc. Domestic pharmaceutical companies from this region play a very important role in China and export in big quantity to other countries all over the world.
2	Southern China	Southern China consists of Guangdong (Guangzhou as its capital city and Shenzhen city), Hainan Provinces, and Guangxi Autonomous Region. Located in Southern China, the Pearl River Delta (PRD) has been one of the fastest growing economic development regions in the world since the 1980s.
3	Northeastern China	Northeastern China consists of Heilongjiang, Jilin, and Liaoning provinces.
4	Northern China	Northern China consists of Beijing City, Tianjin City, Hebei, Shandong, Shanxi (Taiyuan) provinces, and Inner Mongolia Autonomous Region. Mainly located in the Northern China region, Bo Sea Delta is the third fastest developing economic area in China. Many MNCs have regional HQs or subsidiaries there, and domestic pharmaceutical companies are quite strong, especially in API.
5	Central China	Central China consists of Hubei, Hunan, Henan, and Jiangxi provinces.
6	Northwestern China	Northwestern China consists of Qinghai, Shanxi (Xi 'an), and Gansu provinces, Ningxia, and Xinjiang Autonomous Regions.
7	Southwestern China	Southwestern China consists of Sichuan, Yunnan, and Guizhou Provinces, Tibet Autonomous Region, and Chongqing City.
8	Hong Kong SAR	It is estimated that there are about 150 biotechnology-related companies in Hong Kong with their business targeting pharmaceuticals, medical or healthcare products of traditional Chinese medicine origin, and medical devices and diagnostics.
9	Macau SAR	There is only one internationally known pharmaceutical manufacturer, "Hovione" in Macau.
10	Taiwan	Number of Product Items: 12,189. Market Value: $3.2 Million. Taiwan has a small, but fast-growing pharmaceutical industry; there are a large number of manufacturers, but they are concentrating on producing generics, OTC products, and Chinese medicines.

Interview with Senior Leaders from China's SFDA

An interview with senior leaders from China's State Food and Drug Administration (SFDA) appears in the January/February 2009 issue of *Pharmaceutical Engineering*. This interview discusses the latest developments and achievements in SFDA's activities in drug manufacturing and supervision of drug safety. Participants of the interview include:

- **JiangYing Yan**, Deputy Director, Department of Policy and Regulation, SFDA
- **WenZuo Chang**, Counsel, Department of International Cooperation, SFDA
- **Ai Liu**, Liaison Officer, Department of International Co-operation, SFDA
- **QingWu Guo**, Deputy Director, Division of Drug Manufacturing Supervision, Department of Drug Safety and Inspection, SFDA
- **JianHua Ding**, Director, Division of Chemical Drugs, Department of Drug Registration
- **Zhongzhi Qian**, Professor, Director, Chinese Pharmacopoeia Commission
- **Lili Cao**, Director, Division of External Co-operation, CCPIE, SFDA

Strengths and Challenges Facing the Industry

Continued from page 6.

This is by no means a situation unique to China; however, only in very few other cultures are traditional medicines in such prevalent use.

Product Recall

The mechanism for product recall is currently undergoing some serious reforms in China. Measures that have been implemented in other sectors, such as food and toy manufacturers, are now being considered for the pharmaceutical sector. The essence of this change is that manufacturers would be made to instigate and finance their own product recalls. This is a radical reform of the industry in China, but brings the sector in line with more established industries around the world. These new regulations are envisaged to make voluntary recalls mandatory for firms, with state ordered recalls used only in the event of this not happening, which would then be subject to firms being fined for non compliance.

This type of reform can be further seen to enhance companies taking greater responsibility for the raw material supply chain, drug safety and quality testing prior to release into the marketplace.

Validation

Some aspects of validation have been very quickly accepted and taken on board by many Chinese manufacturers. The main reason for this is the technologically advanced local employees. Purchasing of production equipment is seen as one of the fundamental cost aspects of any new production environment. So since equipment is an easily tangible cost center, validation of equipment is seen as a beneficial step in added value engineering.

However, this does not automatically cross over in other areas of validation usually seen as fundamental in assuring a complete production facility. Process validation as a whole is still in its infancy and laboratory based validation activities incur their own inherent problems. Standard QC testing, for batch release of product, has not in the past been permitted under Chinese drug law for local mainland companies. This has led to a lack of on site laboratory facilities and as such analytical testing, stability studies, and laboratory method development and validation has been outsourced.

Conclusion

It can be seen that a great many changes are taking place in the pharmaceutical industry at present in China. While models for this change have been derived from industry and industry partners elsewhere in the world, the challenges facing China are uniquely Chinese.

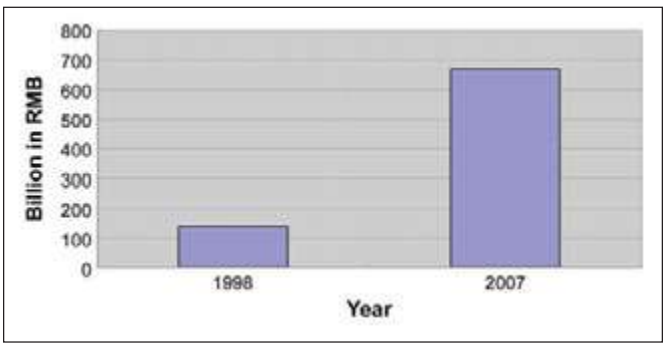
Time and red tape may be factors that limit some operations from being attractive to conduct in China, but as can be seen from measures being considered by the ministry of health and other governing bodies, it may only be a matter of time before this situation is resolved. PE

Size and Growth of the Industry

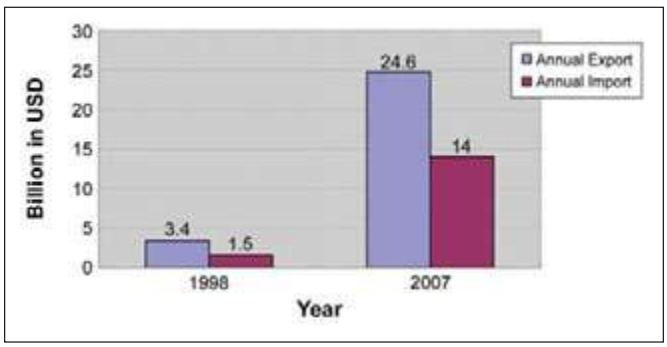
Recent years have witnessed a marked increase in the total output value and trade volume of China's pharmaceutical industry, which is divided into seven categories: 1. Chinese patent medicines, 2. prepared slices of Chinese crude drugs, 3. bulk chemical drug substances, 4. chemical drug preparations, 5. biologicals, 6. medical devices, and 7. hygienic materials. Their total output value rose from 137.1 billion Yuan in 1998 to 667.9 billion Yuan in 2007. From 1998 to 2007, the export trade volume of pharmaceutical industry increased from $3.4 billion to $24.6 billion, and the import trade volume from $1.5 billion to $14.0 billion.[1]

The following contents are presented in the charts below:

- Annual total production value of the industry for 1998 and 2007
- Annual export and import for 1998 and 2007 PE



Annual total production of pharmaceutical industry in China mainland.



Annual export and import of pharmaceutical industry in China mainland.

Market Size Breakdown by City Tier

According to the various economic stature of each city, the cities of China are divided into three different tiers:

Tier 1

Beijing, Shanghai, and Guangzhou comprise the top tier cities, which account for 21% of the total pharmaceuticals market in China.[2] With more than 7 million populations each, three cities' total GDP represent 11.48% of China's in 2006. The average annual per capita expenditure on healthcare was $143 in 2006, among which $70 was medicine expenses.[3]

Tier 2

The second tier cities include cities from the Yangtze River Delta hub, the Pearl River Delta hub, and the hubs of Central and Northeast China, where pharmaceutical market size doubled in the past five years.[2] Take a group of 13 of China's main second tier cities, for example.[4] While this group of cities comprises only 8% of China's total population, it accounts for more than 17% of China's total GDP. The group of cities' average expenditure on healthcare per capita was $112 in 2006, a little lower than the level of top tier, but much higher than the level of the whole country – $88.[3]

Second tier cities.

Tier 3

Other mid to small-sized cities comprise the third tier cities. Due to the lower income and less attention to healthcare, annual per capita expenditure on healthcare is less than other tier cities. Taking 11 cities for example,[5] the average annual expenditure on healthcare is $82.[3]

Academic Affiliations

There are many pharmaceutical-related academic affiliations in China. The following is a partial list of key academies and universities/colleges.

Key academies include China Academy of Science (CAS), China Academy of Medical Sciences (CAMS), China Academy of Chinese Medical Sciences (CACMS), Shanghai Institute of Pharmaceutical Industry (SIPI), Tianjin Institute of Pharmaceutical Research (TIPR), and Chongqing Pharmaceutical Research Institute (CPRI).

Under CAS, is the Shanghai Institute of Materia Medica (SIMM), Chengdu Institute of Biology (CIB), Shanghai Institute of Organic Chemistry (SIOC), and Kunming Institute of Botany (KIB).

Located in Beijing, the China Academy of Chinese Medical Sciences (CACMS) was established in 1955. At present, is the largest research organization on TCM throughout the country. There are 13 institutes, six hospitals, as well as the Graduate School, the Publishing House of Ancient Chinese Medical Books and the Journal of TCM.

The staff of CACMS is more than 4,000, including 3,200 professionals in various fields. In addition, three WHO collaborating centers for traditional medicine have been set up through the cooperation and joint efforts between WHO and CACMS in the fields of clinical medicine and information, acupuncture, and Chinese materia medica. Moreover, the World Federation of Acupuncture and Moxibustion Societies (WFAS), the Chinese Association of Integration of Traditional and Western Medicine (CAIM), and the Chinese Association of Acupuncture and Moxibustion (CAAM) are also attached to the Academy.

Over the past 50 years, remarkable achievements have been obtained in the Academy in the fields of basic theory of TCM, prevention and treatment of prevalent diseases, and R&D for new herbal medicines. In addition, the National Clinical Trial Center for New Herbal Medicines (GCP), the National Standardization Laboratory for Chinese Herbal Pharmacology, China Center for TCM Literature Retrieval and P3 Laboratory, the national Center for Evaluation on Safety of Herbal Medicines (GLP), and the National Development Research Center for Herbal Compound Medicine are all located in the Academy.

As an important window of external cooperation and exchange of TCM, extensive and friendly communications and links have been established between CACMS and the medical circles, research institutions, higher learning universities, pharmaceutical companies, and non-governmental societies of more than 100 foreign countries and regions. Now, CACMS enjoys more and more popularity in the medical circle of traditional medicines throughout the world. More detailed information can be found at http://www.cacms.ac.cn.

Institute of Materia Medica, Chinese Academy of Medical Sciences, and Peking Union Medical College is one of the primary institutions for drug research in China. It was founded in 1958. There are more than 400 employees, among them,

Continued on page 11.

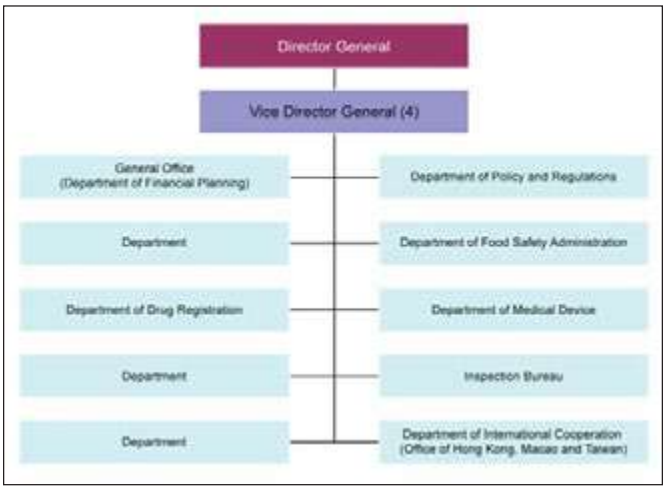
Regulatory Agencies in Greater China

Regulatory responsibilities in Greater China are split between a number of organizations on the mainland and other regions. These include the State Food and Drug Administration (SFDA), the Ministry of Agriculture, the pharmaceutical service of the Department of Health of the Hong Kong Special Administrative Region (HKSAR), and the Macau Health Authority with the Departamento dos Assuntos Farmacêuticos (DAF) or Pharmaceutical Affairs Department. Taiwan Regulatory Affairs are controlled by the Taiwan Department of Health (DOH).

China SFDA

The China SFDA is responsible for the following activities:

- Formulating policies and schemes and monitoring the implementation of safety, supervision, and management of drugs, medical instruments, cosmetics, and consumer food goods. Participating in drafting relevant laws and regulations as well as relevant authorities' stipulations.
- Formulating management practice on Chinese Traditional Medicine (CTM) and medicine of ethnic minorities, and organizing the implementation; drafting quality standards on CTM and medicine of ethnic minorities; organizing the establishment of quality management practice on CTM and regulations on processing procedures of Chinese herbal medicine drinks, and supervising the implementation; organizing the implementation of a protection system on CTM varieties.
- Supervising and managing sanitation licenses of said industries.
- Organizing the inspection and penalty of illegal activities in said industries.
- Establishing safety management and quality practices, safety investigation, technical supervision, and inspection in said industries.
- Administering registration of drugs and medical instruments; drafting national standards on drugs and medical instruments and supervising the implementation; organizing the inspection on Adverse Drug Reactions (ADR) and medical instruments.
- Guiding local food and drug management, such as administration, emergency, inspection, and IT construction.
- Drafting and improving the qualification system for Licensed Pharmacists; directing and supervising the registration of licensed pharmacists.
- Undertaking international exchanges and cooperation on food and drug administration.



SFDA organizational structure.

Ministry of Agriculture

The Ministry of Agriculture is responsible for the following activities:

- Drafting the laws, rules, and regulations regarding veterinary, veterinary drugs, and animal quarantine; and to define and implement related policies.
- Organize supervision, inspection, completion, and acceptance of related industry projects.
- Defining the growth plan of veterinary and veterinary drug regulation system and organizational development; and to implement the policies on veterinary and veterinary drugs.
- Engaging in animal health-related issues, the supervision and regulation on the drug residue, and the quality and safety of animal and animal products.
- Supervising and regulating veterinary drugs and medical devices, as well as import and export regulations.
- Developing and amending the directories of drug and feed additives as well as forbidden drugs and other compounds.
- Drafting animal health codes; prepare and publish the national codes for veterinary drugs, the standards of residue limits, and the standards of residue testing; and to engage in the implementation.
- Undertaking the negotiation and execution of multilateral and bilateral agreements on veterinary, veterinary drugs, and animal quarantine.

The Pharmaceutical Service of HKSAR

The Pharmaceutical Service of the Department of Health of the Hong Kong Special Administrative Region (HKSAR) is responsible for the registration and licensing of pharmaceutical products and manufacturers, importers and exporters, wholesalers and retailers.

Good Manufacturing Practice (GMP) has been enforced and implemented in pharmaceutical and food industries to ensure the products can meet the standard and safety requirements of the international standards implemented in the US, Europe, and Australia.

The HKSAR has supported the development and have plans to monitor and control the Traditional Chinese Medicine and integration into the mainstream health service systems.

Academic Affiliations

Continued from page 9.

there are three members of the Chinese Academy of Sciences and two members of the Chinese Academy of Engineering. Fifty of these experts receive governmental funding.

The main task of the Institute is searching for new drugs for treatment of commonly occurring diseases that seriously threaten people's health. These include cancer, cardio- and cerebral vascular diseases, inflammatory and immunological disease, hepatitis and other viral diseases, disorders of the nervous system and retrogression of old age, etc. At the same time, emphasis is put on the application and development of modern medical theory and high technology.

Since establishment of the Institute, more than 270 prizes have been awarded for its research achievements. More than 100 new drugs have been developed. Since the research fund system was established in China in 1986, the Institute has been granted approximately 500 research subjects of all kinds. Three thousand one hundred scientific papers and 115 monographs have been published by staff members. More than 135 patents, both domestic and abroad, have been applied for.

Scientific and technological cooperation has been established with pharmaceutical companies, universities, and research institutes from more than 30 countries and areas in the world, such as Taisho Pharmaceutical Co. Ltd. (http://www.taisho.co.jp/en/), Les Laboratoires Servier (http://www.servier.com/), and Bayer AG (http://www.bayer.com/en/homepage.aspx). More detailed information could be found at http://www.imm.ac.cn

Key Universities/Colleges Include China Pharmaceutical University (CPU), Shenyang Pharmaceutical University (SPU), Peking University Health Science Center (PUHSC), Beijing University of Chinese Medicine (BUCM), Sichuan

Continued on page 12.

Regulatory Agencies

Continued from page 10.

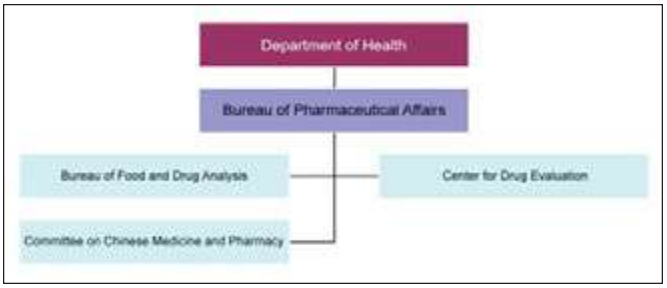
Macau Health Authority and DAF

Responsibilities for the Macau Health Authority and DAF include:

- Developing the quality standards and conditions for license issuance concerning the production, wholesale, and supply of pharmaceuticals and conventional and regular drug products.
- Granting licenses to pharmaceutical manufacturers, importers, and wholesalers.
- Granting licenses to traditional Chinese medical facilities.
- Monitoring the compliance of rules and regulations on quality production, distribution, and supply of pharmaceuticals and conventional and regular drug products, subject to laws and regulations.
- Inspecting and determining whether the efficacy, safety, and quality of pharmaceuticals and conventional and regular drug products meet the standards, and notify the healthcare agency in case of any potential hazards to public health.
- Imposing proper penalty on the above-mentioned defects.
- Registering and updating all pharmaceuticals permitted to distribute in Macao.
- Evaluating the applications for pharmaceutical registration.

Taiwan Department of Health (DOH)

1. Department of Health (DOH) – Pharmaceutical registration/drug approval, review of free sales certificates and plant master files
2. Bureau of Pharmaceutical Affairs (BPA) – Policy making and Rule Setting for DOH
3. Bureau of Food and Drug Analysis (BFDA) – Quality Control of Food and Drug; GMP Inspection for DOH
4. Centre for Drug Evaluation (CDE) – Full-time professional reviewers, in-house reviewing organization for DOH/BPA
5. Committee on Chinese Medicine and Pharmacy – provide technical advice and consultation to DOH/BPA



Taiwan Department of Health (DOH) organizational structure.

Sources for Further Information

1. China State Food and Drug Administration – http://www.sfda.gov.cneng
2. China ministry of agriculture – http://www.agri.gov.cn
3. Hong Kong Department of Health – http://www.dh.gov.hk/eindex
4. Macau Ministry of Health – http://www.ssm.gov.mo/design/home
5. Taiwan Department of Health – http://www.doh.gov.tw/english

Academic Affiliations

Continued from page 11.

University West China Center of Medical Sciences, School of Chemical Engineering. CPU and SPU are the only two comprehensive pharmaceutical universities in China.

The China Pharmaceutical University (CPU), originally the National Pharmaceutical School founded in 1936, is one of the "211 project" key universities affiliated with the Ministry of Education. CPU was China's first independent school of pharmacy and one of the biggest multi-specialty universities of pharmacy with the complete pharmaceutical subjects in China. Located in Nanjing, CPU consists of seven schools, including the School of Pharmacy, the School of Traditional Chinese Pharmacy, the School of Life Science and Technology, the School of International Pharmaceutical Business, the School of Continuing Education, the Zhenjiang Vocational School, and the School of Basic Sciences, three departments, including the Department of Social Sciences, the Department of Physical Education, and the Department of Foreign Languages, six research institutes and seven research centers. For details, visit http://www.cpu.edu.cn/English/xin2intoductions1.htm.

Shenyang Pharmaceutical University (SPU) has developed into a multi-disciplinary, multi-level, and multi-form pharmaceutical institute of higher learning. It consists of Schools of Pharmacy, Pharmaceutical Engineering, Traditional Chinese Medicines, Business Administration, Basic Courses, and Adult Education. The University has been authorized to confer Master's and Doctor's degrees and to enroll students from areas of Hong Kong, Macao, Taiwan, foreign countries, as well as recommended students from senior middle schools for admission to the University. Currently, the total students of all levels are more than 7,000. At the University, there is an Institute of Materia Medica, an Institute of Pharmaceutical Education of Higher Learning, a computer center, an audio-visual education program center, a center of instrumental analysis, a botanic garden of medicinal herbs, and a subsidiary pharmaceutical factory, etc. For details, visit http://www.syphu.edu.cn/en/about/about.htm.

Peking University Health Science Center (PUHSC) is located in Xueyuan Rd., Haidian District, a cultural area with many universities. It is in the center of the well-known Zhong Guan Cun Hi-Tech Zone. PUHSC is a well-structured, multi-disciplined comprehensive medical education palace with a long history. PUHSC offers a full range of courses for eight specialties, including basic medical sciences, clinical medicine, preventive medicine, stomatology, pharmacy, nursing, medical laboratory diagnosis, and biomedical English. It has 47 accredited doctoral programs and 59 Master's programs. In addition to offering undergraduate and graduate programs, it also plays an active role in continuing education. PUHSC hosts six postdoctoral programs. PUHSC has six schools, namely, the School of Basic Medical Sciences, the School of Pharmaceutical Sciences, the School of Public Health, the School of Nursing, the School of Distance Education, and the Faculty of Foundation Education. For details, visit http://www1.bjmu.edu.cn/E_bjmu/html/about/about.html.

The Center for Pharmaceutical Information and Engineering Research (CPIER) of Peking University operates the Graduate Program of the International Pharmaceutical Engineering Management of Peking University. The center was

Concludes on page 14.

Pharmaceutical Engineering Program: Education Opportunities and Challenges in China's Pharmaceutical Engineering: 1998-2008

by Cheng Qiang and Song Hang

In China mainland, paralleled with the establishment of the State Drug Administration, the pharmaceutical engineering program was authorized and added to the China's Higher Education Bachelor Program Catalogue amended by the State Education Committee in 1998. In this revised catalogue, there are only four Bachelor's programs covering the pharmaceutical system fields, instead of the more than 10 previous programs. They include a BS in Pharmacy, a BS in Traditional Chinese Medicine, B Eng in Pharmaceutical Engineering, and BS/B Eng in Pharmaceutics.

Unlike the pharmacy education, pharmaceutical engineering is still a relatively new engineering field in academia worldwide. However, this program has grown substantially in its first decade and rapidly has been attracting more and more fresh students. The number of universities and colleges with established pharmaceutical engineering bachelor programs was 34 in 1999; 59 in 2002; 98 in 2003; 121 in 2004; and 148 in 2007, meanwhile the undergraduate enrollment for the pharmaceutical engineering program increased dramatically from 1165 in 1999 to almost 10,000 in 2008.

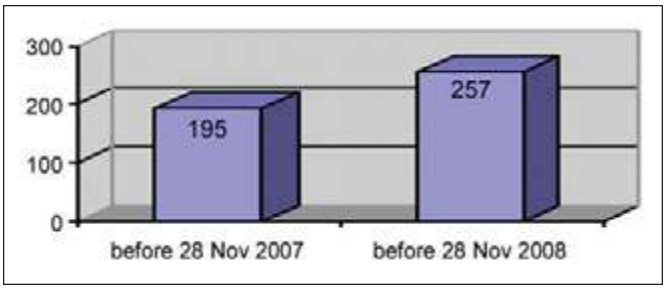
It is critical to be able to define its common knowledge, core curriculum, range of activities, and professional skill to face the growing challenges in drug discovery, development, manufacturing, and distribution.

The Subcommittee of Pharmaceutical Engineering, Teaching Advisory Committee for Chemistry and Chemical Engineering of Ministry of Education have played an important role in this engineering education field and the need for the effective interaction between academic universities and the pharmaceutical industry will continue to be a key driver in the continual success of engineering education in China.

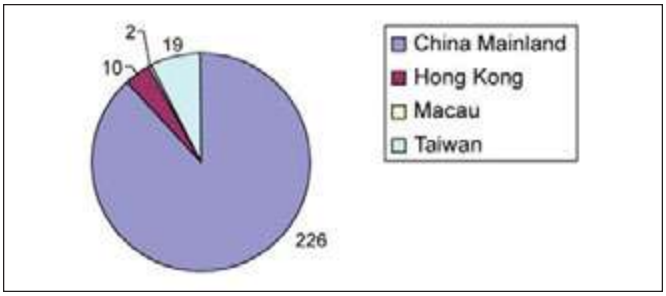
A Brief Introduction to the ISPE China Affiliate

Membership

The ISPE China Affiliate has grown to 158 Chinese members since the ISPE China Office began the official operation in April 2008.



Growth of membership in ISPE China.



Current membership breakdown by region.

Volunteer Leaders

The ISPE China Advisory Committee consists of about 30 members as listed below:

Mr. Jason Tang (Chairman), Prof. Song Hang (Co-Chairman), Mr. Mars Ho, Dr. Zhao Chun Hua, Mr. Gustavo A. Fuente, Mr.Yang Huichuan, Ms. Cao Lili, Ms. Liangqiu(Tracy) Li, Mr. Allan Hong, Mr. Zheng Qiang, Mr. Kam Liu, Mr.Bowie Soe, Ms. Qi Ying, Mr. Meng Yu, Mr. David Sun, Mr.Sun Xiaobing, Ms. Yunxia(Sophia) Zhao, Dr. Beatrijs Van Liedekerke, Dr. Xu Jia, Mr. Jonathan Woodburn, Mr. Tommy Li, Mr. Cheng Qiang, Mr. Lu Tao, Mr.Shih Younan, Mr. Makoto Koyazaki, Ms. Lin Hong, Ms. Wu Qing, Mr. Bono Tang, Mr. Sui Jingo, Mr. Yang Haifeng, Mr. Michael Lee, and Mr. Morten Stenkilde.

Volunteer leaders of the ISPE China Advisory Committee.

Student Chapter

The first Student Chapter in China was established at Sichuan University in November 2008 with 111 student members.

Professor Song Hang, Faculty Advisor of the ISPE Student Chapter of SCU, and a student representative attended ISPE-CCPIE China Conference 2008.

Student chapter meeting at Sichuan University.

Professor Song Hang and a student representative attended the ISPE-CCPIE China Conference.

Conference

ISPE-CCPIE China Conference 2008 was successfully held in conjunction with the 13th China International Pharmaceutical Industry Exhibition (China Pharm 2008) in Beijing from 11-12 November, 2008. More than 20 renowned international and local speakers, including representatives from the FDA and SFDA shared latest regulatory information and cutting-edge technical knowledge with more than 250 delegates.

ISPE will hold a conference in China annually. The 2009 conference will be held in Shanghai.

Training Courses

A curriculum designed to meet the needs of the Chinese pharmaceutical industry will be offered over the next three years. One series of training courses will review the US FDA pre-approval and post-approval phases for exporting pharmaceuticals to the United States.

Concludes on page 14.

Academic Affiliations

Continued from page 12.

established in June, 2006, under the leadership of Dr. Qiang Zheng, Center Director and a Professor at the College of Engineering of Peking University. The center engages in scientific research and educational activities in the areas of pharmaceutical engineering management, drug clinical data management and analysis, in order to teach practical knowledge and to provide science-based decision-making support for the pharmaceutical industry and government regulatory agencies, as well as to provide quality drug usage information to the public. For details, visit http://www.cpier.pku.edu.cn.

Sichuan University has the widest coverage of disciplines and the largest scale of operation in West China, and is rated the "Top University in Western China." It incorporated three famous universities, namely, the former Sichuan University, Chengdu University of Science and Technology (CUST), and West China University of Medical Sciences (WCUMS) since 1994 and 2000. Over more than 100 years of development, the University has laid a sound foundation and has built a high reputation in academic research and learning. It has great potential in the field of Chinese language and history, mathematics, life science, polymeric science and engineering, electrical engineering, chemical engineering, leather science and engineering, water resource and hydropower, stomatology, clinical medicine, pharmaceutical science and engineering.

The pharmaceutical scientific and engineering education in this University can be traced back to 1932 when the Department of Pharmacy of College of Science of West China Union University was founded. At present, Sichuan University provide both the BS program in pharmaceutical science by the School of Pharmacy and BEng program in pharmaceutical engineering by the School of Chemical Engineering. There are currently more than ten Master's and Doctoral degree programs in pharmaceutical science and engineering, mainly from the School of Pharmacy, School of Chemical Engineering, and State the Key Laboratory of Biotherapy of Human Diseases. For details, visit http://www.scu.edu.cn.

Beijing University of Chinese Medicine (BUCM), founded in 1956, is one of the earliest established TCM institutions for higher learning in China. It is the only TCM university that entered the "211 Project" key universities affiliated with the Ministry of Education. At present, the University consists of the School of Preclinical Medicine, the School of Chinese Materia Medica, the School of Acupuncture, Moxibustion and Tuina, the School of Administration, the School of Traditional Chinese Nursing, the International School, the School of Distance Education, the School of Continuing Studies, the School of Chinese Clinical Medicine, the Department of Humanities and Social Science, and the Department of Chinese Medicine for Taiwan, Hong Kong, and Macao. It also has three affiliated hospitals and one pharmaceutical plant. For details, visit http://www.bucm.edu.cn.

A Brief Introduction to ISPE China

Continued from page 13.

Bob Best, ISPE President and CEO at the ISPE-CCPIE China Conference.

Other Activities

ISPE Communities of Practice (COPs): COPs will be launched in the Chinese language.

Publications Translation: ISPE publications and technical documents will be translated into Chinese.

More information of ISPE Greater China will be available at www.ISPE.org.cn which is updated weekly.

ISPE China Affiliate Web page.

Pharmaceutical Associations and Organizations in China

China-Regional

Beijing Branch of the Chinese Medical Association
www.chinamed.com.cn

China Association of Traditional Chinese Medicine (CATCM)
www.catcm.org.cn

China Quality Association for Pharmaceuticals (CQAP)
www.cqap.org.cn

Introduction of China Pharmaceutical Association of Plant Engineering (CPAPE)
www.cpape.org.cn

China Pharmaceutical Enterprise Management Association (CPEMA)

China Medicine Health Products Marketing Association (CMHPMA)
www.cmhpma.org.cn

National Institute for the Control of Pharmaceutical and Biological Products (NICPBP)
www.nicpbp.org.cn

Chinese Institute of Food Science and Technology (CIFST)
www.cifst.org.cn

China Food and Packaging Machinery Industry Association (CFPMA)
www.chinafpma.org

China Dairy Industry Association (CDIA)
www.cdia.org.cn

China Association on Monitored and Controlled Chemicals (CAMCC)

China Chemical Industrial Equipment Association (CCIEA)
www.cciea.com

China Health Food Industry Association

Tianjin Pharmceutical Profession Association (TPPA)
www.tppa.sina.net

Tianjin Packaging Technology Association

Shanghai Medical Association
www.shsma.org.cn

China Federation of Industry Beauty Cosmetics Chamber of Commerce

Liaoning Packaging Technology Association

Huayin Media Group China Packaging Federation

Henan Packaging Technology Assciation (HPTA)

Hebei Medical Association
www.hebma.com

Hangzhou Pharmaceutical Industry Association

Dalian Packaging Technology Assciation
www.dalianpack.net

Beijing Association of Integrative Medicine
bjaim.itcmedu.com

Beijing Zhongguancun Enterprise Association of Biotech. and Pharma.
www.zgceabp.org.cn

Beijing Association of Acupuncture-Moxibustion

Beijing Medical and Health Sector Overseas Friendship Association

Beijing Pharmaceutical Association

Beijing Pharmaceutical Profession Association (BPPA)
www.bppa.org.cn

Beijing Pharmacists Association

Beijing Packaging Technology Assciation

Beijing Biomedical Engineering Society

Beijing Bioengineering Association
www.bjbio.org.cn

Beijing Rehabilitation Medical Association

Beijing Hailianweiye Cultural Exchange Center

China-Nationwide

Shandong Daily Chemical Industry Association Committee on Professional Beauty Cosmetics
www.sdbdexpo.com/lianxi.htm

Beijing Health Products Association

References

1. Translated from a White Paper on "Drug Safety Administration Status in China Mainland," issued by China State Council News Office, 18 July 2008.
2. "Rapid Growth of Pharmaceutical Economy in China," Pharmaceutical Economy, 18 December 2007.
3. National Bureau of Statistics, 2007, Exchange rate: US $1.00=RMB7.00.
4. Harbin, Dalian, Qingdao, Tianjin, Xian, Wuhan, Hangzhou, Ningbo, Nanjing, Chongqing, Kunming, Shenzhen, and Xiamen.
5. Zhengjiang, Nantong, Yangzhou, Taizhou, Jiangmen, Zhongshan, Huizhou, Zhaoqing, Tangshan, Weihai. Jiaxing.

Acknowledgements

The developers of the China Country Profile would like to thank the following authors: Bowie Soe, Bono Tang, CCPIE under SFDA, Cheng Qiang, David Sun, Gao Ye, Huacheng Wei, ISPE China Office, Jiang Hai, Kam Liu, Lin Hong, Makoto Koyazaki, Song Hang, Sophia Zhao, Sun Xiaobing, Xielong Luo, Xuelian Xu, Xu Jia, Wu Qing, Yang Hui Chuan, Yang Dan Bo, Yao Wen, Zeng Yi, and Zheng Qiang.

The developers also would like to thank the following reviewers for their contributions: Beatrijs Van Liedekerke, Jason Tang, Jonathan Woodburn, Michael Lee, Qi Ying, and Zhao Chunhua.

- Master Planning
- Concept Design
- Basic Design
- Engineering
- Construction
- Commissioning
- Procurement
- Validation

We've been delivering successful projects in China since the 1970s. With established operations in Shanghai and Beijing, we have a strong capability in the region, to support our pharmaceutical customers.

We work with Chinese Design Institutes and complement their project execution approach. We work with civil construction companies and plant erection contractors. We understand Chinese government procedures and the approval process.

We know China. We know pharma.

Contact us locally:
1-16 POS Plaza 1600 Century Avenue
Pudong New Area Shanghai 200122
(+86) 21 5058 2626
fw_pharma@fwc.com
www.fwc.com

FOSTER WHEELER

PHARMACEUTICALS - BIOTECHNOLOGY - HEALTHCARE

CHILE • CHINA • FRANCE • INDIA • IRELAND • ITALY • MALAYSIA • RUSSIA • SINGAPORE • SOUTH AFRICA • SPAIN • SWITZERLAND • THAILAND • TURKEY • UK • US

ENGINEERING PHARMACEUTICAL INNOVATION ISPE

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2009,
Vol. 29 No. 1

www.ISPE.org

ISPE Starts Science and Technology Initiative in 2009

Project Encourages Greater Emphasis on Science and Technology to Advance Industry's Manufacturing and Distribution Performance

by Charles Hoiberg, Chairman of the ISPE International Board of Directors

Our global, not-for-profit Society that we have come to love during its 28 years of existence has grown close to 25,000 members in more than 90 countries and whose members are employed in industry, academia, and government as engineers, scientists, suppliers, and as regulators. So, for a simple chemist like me, this will be a complex operation to help manage. But, ISPE has gained prestige globally, in large part, because it has so many dedicated, talented, and engaged Members like you.

However, there are many significant challenges that will test the Society and our Members in the year ahead. One only needs to look at current stock prices for many of the leading firms, or the list of innovator drug products coming off patent, or the decreasing number of new drugs in the development pipeline to understand some of the pressures the industry is facing. This is in addition to the overall state of the global economy. Most firms are thoroughly examining how to reduce overhead and how to cut drug development and manufacturing costs. These troubling trends will undoubtedly have an impact on ISPE.

Another challenge is that as firms relocate more of their drug development and manufacturing sites to the Asia-Pacific region, ISPE Members' needs will change. We must react to this and design our offerings accordingly.

It is also evident that some traditional new chemical entity firms are realigning or expanding their business interests into the generic and the biotechnology areas. ISPE is not as well known in these sectors, but our tools and services are equally valuable to professionals in these fields. The Society must expand its reach into these areas.

Many large firms are also outsourcing more and incorporating many other parties, vendors, and suppliers into their business plans. ISPE needs to better connect with these professionals and more fully engage them.

We must ensure that ISPE is the professional development organization of choice. In other words, we must excel at being the best in serving our Members.

I strongly believe that ISPE can be a major resource to the industry and its regulators in these challenging times. Let me give you an important example. The approaches that many pharmaceutical firms are taking to develop and manufacture drugs are changing, in part due to the recent ICH Quality Guidelines Q8, Q9, and Q10.

It is assumed that as the business case for Quality by Design (QbD) is better appreciated, QbD will be increasingly implemented and the goal of achieving the "desired state" will be obtainable. The implementation of QbD also will impact and result in dramatic changes in the ways regulatory assessments and inspections may be performed.

Based on these realities, ISPE leaders held a strategic discussion during our annual planning retreat in July to develop a "Science and Technology" initiative to meet these needs. The vision is that ISPE will act as an integrator for all pharmaceutical disciplines to assist industry and regulators in advancing manufacturing science in order to achieve excellence in developing drugs and in pharmaceutical production.

We have defined Science and Technology as the collective term for the umbrella project that integrates the Society's understanding and advancement of manufacturing sciences. Manufacturing sciences is defined by ISPE as the integrated application of scientific knowledge, technical innovation, and

Concludes on page 75.

Global Suppliers Directory and More Available on INTERPHEX365 Web Site

Sponsored by ISPE, INTERPHEX365 (www.interphex365.com) provides a global online community where life science professionals can search an online global directory of industry suppliers, source active projects, and communicate directly with suppliers.

Users can connect with other professionals and find solutions to problems through online community networking, industry education, white papers, and Web seminars, as well as get the latest industry and regulatory news. Content from the pharmaceutical and life science industries is free with registration and is easily searchable and readily accessible year-round.

High-impact, low-cost advertising opportunities are available on INTERPHEX365. For more information, contact Dave Hall, ISPE Director of International Sales by tel: + 1-813-960-2105 Ext. 208 or email: dhall@ispe.org.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

ISPE-CCPIE Conference in China a Success

A very successful ISPE Conference was held in Beijing 11 to 12 November in cooperation with the China Center of Pharmaceutical International Exchange (CCPIE), an affiliate of the State Food and Drug Administration (SFDA).

The Conference was oversold with more than 260 delegates and many registrations had to be rejected due to venue capacity. The smooth delivery of the Conference resulted in positive feedback from delegates as they enjoyed one day of plenary sessions and a keynote address; one day for three parallel sessions on biotechnology, GAMP 5, and validation; and an elegant dinner reception for professional networking.

In addition, there were more than 20 renowned international speakers who delivered presentations. Keynote speakers included Bob Best, ISPE President and CEO; Mr. Bian Zhenjia, Director of Drug Safety and Inspection Department of the SFDA; Steven Wolfgang, Compliance Officer of the US FDA; Bob Tribe, ISPE Asia-Pacific Regulatory Affairs Adviser and Former PIC/S Chairman, and other high level officials from the SFDA, etc.

The Conference was held in conjunction with the 13th China International Pharmaceutical Industry Exhibition (China Pharm) which took place from 12 to 14 November 2008 at the China International Exhibition Centre. Sponsors of the event included DoveBid, Hewlett-Packard, NNE Pharmaplan, Pall Life Sciences, Pharm-Tech Magazine, Rockwell, and Shimadzu.

Bob Best, ISPE President and CEO at the ISPE-CCPIE China Conference.

In addition to ISPE's annual conference in China, CCPIE will cooperate closely with ISPE in a variety of ways, including providing training opportunities for the region. Visit www.ispe.org.cn for more information about conferences, training, and symposiums being offered in China.

Philippines Affiliate Launched

The challenges posed by the soon-to-be implemented ASEAN harmonized registration system for pharmaceuticals as well as dynamic regulatory requirements were some of the factors that prompted industry executives to form the ISPE Philippines Affiliate.

With more than 90 participants from various pharmaceutical companies and academe, the Philippines Affiliate was launched at the Wyeth Training Centre in Makati on 10 October 2008.

Talks about forming the Affiliate started in February 2008 with eight volunteers who saw the value and benefits of ISPE in the country. After eight months of preliminary work, the Affiliate was finally launched in the Philippines.

The board consists of 15 volunteers, all of whom are professionals in the industry and academe. The Affiliate will work in conjunction with ISPE to extend benefits to local members and to promote networking and interaction between professionals within the pharmaceutical industry. The Affiliate also aims to deliver a program throughout the year that is beneficial to members and will address the current concerns/issues within the industry. The Board hopes that the presence of ISPE in the Philippines can help promote and develop a pharmaceutical and engineering infrastructure in the country.

Klara Tisocki, Drug Registration Specialist currently with BFAD as a consultant, and Peter Tan, ISPE Asia Pacific Affiliate Relations Manager, were guests at the launch. Tan gave a brief introduction on the benefits of ISPE membership to the attendees present. The attendees also were encouraged to sign up as volunteers for the different committees within the Affiliate.

Participants from 30 Countries Attend Successful PIC/S-PDA-ISPE Workshop in Geneva

In conjunction with the Committee meeting, PIC/S in partnership with ISPE and the Parenteral Drug Association (PDA) organized an interactive joint workshop on the "Manufacture of Sterile Medicinal Products (EU-PIC/S GMP revised Annex 1)" in Geneva on 13 to 14 November. It was the second time that PIC/S co-organized such a joint event with professional and industry associations.

The meeting was open to both regulators and industry. It was attended by more than 80 participants (among which 50% came from Regulatory Authorities) representing around 30 countries.

The workshop started with a plenary session, including presentations on the interpretation of the revised Annex 1 and on inspection experiences from both regulators' and industry's perspectives. GMP inspectors and industry representatives also participated in practical workshops (case studies) on the capping of vials, media fills (process simulations), the continuous monitoring, the clean area classification and ISO norms, as well as on the sterilization and depyrogenation of contact parts and containers.

The workshop was unanimously considered as a success by both inspectors and industry representatives. More joint workshops will likely be organized with these professional and industry associations in the future.

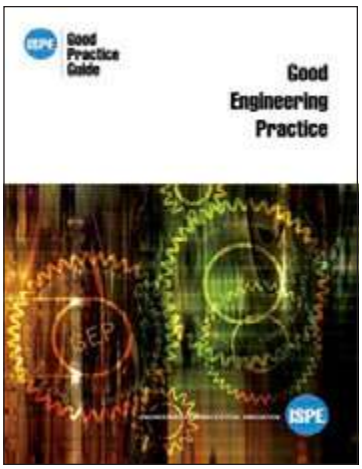
Guide on Good Engineering Practice Released

In November 2008, ISPE released the first edition of the ISPE Good Practice Guide: Good Engineering Practice.

"Good Engineering Practice (GEP) is defined as the minimum engineering methods and standards that are applied throughout the lifecycle of an asset to deliver fit for purpose and cost effective solutions," said Chris Derrett, Chair of the ISPE Good Practice Guide: Good Engineering Practice Task Team.

This Guide covers the complete lifecycle of engineering from concept to retirement. The Guide:

- aims to promote a common understanding of a benchmark definition that could be usefully employed in assessing an individual company's practices
- is aligned with the pharmaceutical industry, recognizing that the GEP core concepts that apply universally through specific practices vary from industry to industry
- identifies key attributes of GEP, including how GEP relates and interfaces with GxP



For additional information and the complete table of contents, please visit www.ISPE.org/publications.

Project Encourages Greater Emphasis on Science and Technology...

Continued from page 72.

quality risk management to deliver product and process understanding.

Product Quality Lifecycle Implementation (PQLI) is an initiative focused on providing guidance on best practice implementation of the concepts described in ICH Guidelines, particularly Q8, Q9, Q10, and the future Q11.

Starting in 2009, Science and Technology will be a system set up within ISPE to work with industry and regulatory leaders worldwide to encourage a greater emphasis on science and technology to advance and enhance the manufacturing and distribution performance of the pharmaceutical industry.

It will generate a Science and Technology pipeline of projects for ISPE to develop, advance, and disseminate to its Members. The initial emphasis will be to promote PQLI and the further development of pragmatic and practical implementation of ICH and related guidelines — such as Q8, Q9, Q10, and Q11 — based on sound scientific, engineering, and business principles.

What has been completed to date are five published papers in the June issue of ISPE's *Journal of Pharmaceutical Innovation* (JPI). What is currently in progress is a case study document led by the Control Strategy group. What our future plans involve are an integration paper, case studies, additional JPI articles, and technical guidance documents.

As implied by the project name, PQLI encompasses the total lifecycle of a pharmaceutical product from development through regulatory approval into commercial manufacturing and finally termination. It also encompasses all manufacturing and production activities, including raw materials, APIs and drug product production, facilities design and operation, and product distribution.

The Society will develop a multi-horizon plan for the Science and Technology initiative through PQLI that ensures a continuous flow of the best of science and technology to all sectors of membership. We think the Science and Technology and PQLI initiatives are good examples of the way ISPE can play an important role in helping the industry and regulatory authorities find practical solutions to move into the future.

Yes, the challenges ahead of us are many, but I am very optimistic that ISPE is adapting its programs and business plans so it will remain a leader, a catalyst of change, an innovator, and a valuable resource to all.

As the ISPE Chairman of the International Board for the next 12 months, I sincerely thank you — the ISPE Members — for the privilege of serving you.

Architects, Engineers – Constructors

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

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

Architects, Engineers – Constructors (cont).

Parsons, 150 Federal St., Boston, MA 02110. (617)-946-9400. See our ad in this issue.

Aseptic Filling

Aseptic Technologies, Rue Camille Hubert 7-9, 5032 Les Isnes, Belgium. +32 81409410. See our ad in this issue.

Cleanroom Products/Services

AES Clean Technology, 422 Stump Rd., Montgomeryville, PA 18936. (215) 393-6810. See our ad in this issue.

Plascore, 615 N. Fairview, Zeeland, MI 49464. (800) 630-9257. See our ad in this issue.

Consultants

Employment Search Firms

Jim Crumpley & Associates, 1200 E. Woodhurst Dr., Bldg. B-400, Springfield, MO 65804. (417) 882-7555. See our ad in this issue.

Filtration Products

MKS Instruments, 5330 Sterling Dr., Boulder, CO 80301. (800) 345-1967. See our ad in this issue.

Siemens Water Technologies, 10 Technology Dr., Lowell, MA 01851. (978) 934-9349. See our ad in this issue.

Homogenizers

GEA Niro Pharma Systems, 9165 Rumsey Rd., Columbia, MD 21045. See our ad in this issue.

Instrumentation

Hach Ultra Analytics, 5600 Lindbergh Dr., Loveland, CO 80539. (970) 663-1377. See our ad in this issue.

Passivation and Contract Cleaning Services

Active Chemical Corp., 4520 Old Lincoln Hwy., Oakford, PA 19053. (215) 676-1111. See our ad in this issue.

Cal-Chem Corp., 2102 Merced Ave., South El Monte, CA 91733. (800) 444-6786. See our ad in this issue.

Concludes on page 78.

Rupture Discs

Fike Corp., 704 SW 10th St., Blue Springs, MO 64015. (816) 655-4546. See our ad in this issue.

Sterile Products Manufacturing

Tanks/Vessels

Lee Industries, PO Box 688, Philipsburg, PA 16866. (814) 342-0470. See our ad in this issue.

Used Machinery

Validation Services

Commissioning Agents, Inc., 1515 N. Girls School Rd., Indianapolis, IN 46214. (317) 710-1530. See our ad in this issue.

Valves

Gemu GmbH & Co., Fritz-Mueller-Str. 6-8, D-74653 Ingelfingen, Germany. +49 7940123-0. See our ad in this issue.

Gemu Valves, 3800 Camp Creek Pkwy., Bldg. 2600, Suite 120, Atlanta, GA 30331. (678) 553-3440. See our ad in this issue.

Vial Traying Systems

Hurst Corp., Box 737, Devon, PA 19333. (610) 687-2404. See our ad in this issue.

Water Treatment

Elettracqua Srl, Via Adamoli 513, 16141 Genova, Italy. +39 0108300014. See our ad in this issu.

Siemens Water Technologies, 10 Technology Dr., Lowell, MA 01851. (978) 934-9349. See our ad in this issue.

ABB **25**
ACTIVE CHEMICAL **79**
AES CLEAN TECHNOLOGY **27**
ASEPTIC TECHNOLOGIES 31
CAL-CHEM CORP. **53**
COMMISSIONING AGENTS **37**
CRB CONSULTING ENGINEERS **3**
JIM CRUMPLEY & ASSOCIATES **78**
EI ASSOCIATES 65
ELETTRACQUA **43**
EMERSON PROCESS MANAGEMENT **51**
ENVIRONMENTAL TECTONICS CORP. 59
FARR AIR POLLUTION CONTROL **2**
FIKE CORP. **49**
GE WATER & PROCESS TECHNOLOGIES 61
GEA PROCESS ENGINEERING **11**
GEMU GMBH **75**
GEMU VALVES **63**
HACH COMPANY **19**
HURST CORP. **78**
IMA ACTIVE **69**
IMA EDWARDS **15**
INTELLIGEN **13**
INTERPHEX **71**
KINETICS **57**
LEE INDUSTRIES **17**
MKS INSTRUMENTS **23**
NNE PHARMAPLAN **80**
OPTIMA MACHINERY **76**
PLASCORE **33**
PARSONS **5**
PHARMACEUTICAL ONLINE 77
PROSCON 73
SIEMENS WATER TECHNOLOGIES **29**
TELSTAR 9
VALIDATION TECHNOLOGIES 39
WESTFALIA SEPARATOR 45
WILDEN PUMP & ENGINEERING 47

more
than engineering

We are determined to support and **improve technologies** and **standards** in the pharma and biotech industries.

Winner of the ISPE award 2008
Company of the Year

Consulting | Engineering | Construction | Validation | Solutions

NNE Pharmaplan is one of the world's leading engineering and consulting companies. We enable pharma and biotech companies to bring products to market with fast, innovative and reliable services.
We employ more than 1500 people at over 20 locations worldwide.

nne pharmaplan®

nnepharmaplan.com

On-Line Exclusive Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
January/February 2009, Vol. 29 No. 1

Brazil

Pharmaceutical Ingredients[1]

Resolution RDC 30 from ANVISA released on 15 May 2008 established that companies which manufacture, import, export, fraction and distribute pharmaceutical ingredients had 6 months to update their files with ANVISA. The recent Resolution RDC 83 on 17 November 2008 from the ANVISA has allowed an extension of 6 months.

Vaccines and Hyperimmune Heterologous Serums[2]

Resolution 73 dated 21 October 2008 regulates the release of Batches of Vaccines and Hyperimmune Heterologous Serums in Brazil. The National Institute for the Quality Control in Health (INCQS – Instituto Nacional de Controle de Qualidade em Saude) will be in charge of approving the release of such biological medicinal products, for their export and will also deliver a Batch Release certificate. This regulation will come into force on 2 December 2008.

Czech Republic

Requirements for Documents on Good Manufacturing Practice[3]

A second version (October 2008) of guidelines summarizing the requirements for GMP documents when submitting a clinical trial application in the Czech Republic has been released. These guidelines are based on § 57 par. 1 and § 62 of Law 378/2007 Coll. on pharmaceuticals, according to which the manufacture of investigational medicinal products and their import from third countries is subject to a manufacturing licence.

The guidelines go through the following topics among others: The manufacturing/import licence for investigational products, GMP certificate for manufacturer/importer/control laboratory, declaration of the qualified person, manufacturing steps and required documents, all manufacturing steps at the territory of EU/EEA, all manufacturing steps (except for batch release) out of EU/EEA or required documents for comparator product which is not further adjusted for the purpose of a clinical trial for instance.

Quality and Safety Assurance in Human Tissues and Cells Intended for Human Use[4]

This guideline establishes detailed requirements for quality and safety assurance in human tissues and cells intended for human use in the Czech Republic. This guideline has been prepared in line with Law 296/2008 and includes national requirements of Decree 437/2002 Coll. on assessment of health capability and extent of examination of living or dead donor of tissues or organs for transplantations.

The guidance covers these following topics among others: Requirements for establishment of quality systems, obtaining tissues and cells and their provision to a tissue institution, requirements for acceptance of tissues and cells, for procedures of their processing, labeling, release, packing, storing, distribution and recalls from distribution, and quality and safety inspections, application for approval of activity, and its changes, and templates of applications, application form for approval of activity of tissue institution, application for approval of activity of sampling institution or application for approval of activity of a diagnostic laboratory as well.

Estonia

Quality Assurance: Good Manufacturing Practice and Inspections[5]

In Estonia, the state supervision over compliance with the requirements to manufacture shall be exercised by the State Agency of Medicines (SAM). After conducting a general inspection in an enterprise belonging to the holder of an activity license for manufacture of medicinal products or a part of such enterprise, the State Agency of Medicines shall, within ninety days (90 days), issue a certificate to the holder of the activity license concerning the conformity of the enterprise with good manufacturing practices if inspection results confirm the conformity. Manufacturers should comply with the following:

1. Presence of adequate facilities, instructed staff and confirmed rules for procedures in terms of sampling, controlling, testing of precursors, packaging materials, intermediate products, products for wholesale and ready products, as well as for checking of environmental conditions for manufacture.
2. Samples of precursors and package materials, intermediate products, products for wholesale and ready drugs shall be taken only by instructed specialists according to the method established and approved by quality control department;
3. Testing methodology shall be validated;
4. Minutes of the control processes can be registered by hands, with the help of registering devices or using both;
5. Active ingredients of ready product shall comply with qualitative and quantitative composition of the product stated in MA associated documentation, be appropriately packaged, labeled and pure as required;
6. Minutes for control results shall be taken, as well as orderly evaluation in terms of complying with quality requirements of materials, intermediate, wholesale products and products ready for use;
7. No one batch can be marketed or purveyed before the competent person has confirmed batch compliance with requirements of MA associated documentation;
8. Enough samples of precursors and products that shall be stored in the final package, excluding cases with very big amount of product in one package shall be left for future to enable analyzing if needed.

Europe

GMP[6]

The EMEA has released on their Web site a Questions and Answers on EU GMP Guide Annexes regarding the Annex 19 Reference and Retention Sample.

Variations[7]

An amendment has been put forward to update Directive 2001/83/EC Varia-

tions. A variation application is an application to amend the contents of the documentation used to support an existing marketing authorization. The types of variations are classified into minor variations (Type IA or Type IB) or major variation (Type II). Alternatively the change may necessitate an extension application. The marketing authorization holder has an obligation to update the marketing authorization by variation applications as new data emerges. This is particularly important for new information that affects the risk-benefit balance.

The document outlines the requirements relating to variations of marketing authorizations approved via the centralized procedure, mutual recognition procedure or decentralized procedure.

The following meetings were held during the period covered by this update:

- The Committee for Medicinal Products for Human Use (CHMP) held its October plenary meeting from 20 to 23 October 2008[8]
- The Committee for Medicinal Products for Veterinary Use (CMPV) held its October meeting on 14 to 16 October 2008[9]
- The Committee for Medicinal Products for Veterinary Use (CMPV) held its November meeting on 11 to 13 November 2008[10]
- The Committee for Orphan Medicinal Products (COMP) held its ninety-fifth plenary meeting on 4 to 5 November 2008[11]
- A joint meeting by TOPRA and the European Medicines Agency – Medicines Legislation within the European Regulatory Network – A review of the Medicines Legislation by the EMEA and National Competent Authorities held on 2 to 3 December 2008.[12]

Israel

GMP[13]

The Israeli Minister of Health has published a new regulation in order to define medicinal product Good Manufacturing Practice in Israel. The new regulation is based on the Pharmacist Ordinance 1981 and states among other topics guidelines on GMP approval and validity, manufacturing control, samples, internal audits, equipment and utilities, contract manufacturers and quality assurance and control. This regulation will come in effect on September 2009 next year.

Japan

Quality and Safety Assurance of Medicines using Human Cells and Tissues Components[14]

The Pharmaceutical Affairs Division of the Health and Hygiene Department in Japan has published on 3 October 2008 a Questions and Answers bulletin on Quality and Safety Assurance of Medicines and Medical Devices Manufactured Using Human Cells and Tissues Components which was issued on 12 September 2008.

Export[15]

The Pharmaceutical Affairs Division of the Health and Hygiene Department in Japan has released a Questions and Answers bulletin on 11 November 2009, about the application for Exporting Medicinal Products.

Latvia

Procedure of Import and Export of Medicinal Products[16]

Revised regulations determine the procedures for import and distribution of medicinal products in Latvia and export thereof from Latvia, as well as requirements for opening and operation of medicinal product wholesalers. Only Medicinal Products recognized and registered as such shall be subject to trade. A qualified person shall ensure that all trade operations are legal. Data on the concerned products shall be kept at least 5 years, 10 years in the case of psychotropic and narcotic substances on a secure support. Medicinal products may be imported into the territory of Latvia or exported from Latvia if the wholesaler has an import or export permit. The State Agency of Medicines is entitled to import medicinal products (standard samples, medicinal product ingredients) which are intended for testing. Medicinal products may be imported from third countries only through customs points where Sanitary Border Inspection controls are ensured. The importer of the medicinal products shall ensure that at least one qualified person is permanently and continuously at his or her disposal.

Outside pharmacies importers are allowed to distribute non-prescription medicinal products, which are included in the list approved by the Minister for Health and which:

- are intended for self-treatment,
- comply with the restriction specified by the Minister for Health regarding the strength, maximum single and daily dosage, form, route of administration and packaging size of the medicinal products for distribution outside pharmacies,
- shall retain the status of medicinal products for distribution outside pharmacies,
- do not belong to the groups of non-prescription medicinal products.

The State Pharmaceutical Inspection is entitled to take a decision regarding the prohibition of the supply of medicinal products or batch from the market, which are objects of dispute.

The State Pharmaceutical Inspection shall on a regular basis: control the persons involved, pharmacies and medical treatment institutions, medicinal product wholesalers and medicinal product manufacturing undertakings, wholesale and retail undertakings. After each examination a report shall be drawn up.

Poland

Good Manufacturing Practice[17]

A new decree has been released on 17 October 2008 by the Polish Ministry of Health which provides general and detailed requirement of good manufacturing practice. Manufacturing or import licenses will be delivered after full compliance with these requirements including for instance management of quality, manufacturing site and equipment, quality control, self inspection, manufacturing and analysis on demand, complaints and withdrawal, documentation and personnel.

South Africa

GMP[18]

The Medicines Control Council has released version 3 of the Guide to "Good Manufacturing Practice for Medicines in South Africa" in September 2008.

This update intends to facilitate the removal of barriers to trade in medicinal products, to promote uniformity in licensing decisions and to ensure the maintenance of high standards of quality assurance in the development, manufacture and control of medicinal products. The guidance is also aimed to serve manufacturers by elaborating specific rules adapted to their individual needs.

Comments to this guidance are due for January 2009 and will come into force on 1 November 2009.

Turkey

Wholesale Warehouse of Medicinal Products[19]

The Turkish law on wholesale warehouse of medicinal products dated 20 October 1999 has been amended and articles 4, 9 and 11 updated on 24 September 2008. Topics included in these modifications are warehouse for products storage (MA holder's/manufacturer), the list of entities authorized to be supplied by wholesalers and products forbidden for sale and supply.

United Kingdom

Marketing Authorization Procedures: Renewal[20]

Based on the requirements of 2005, marketing authorizations had to be renewed every five years. Under the revised requirements, a marketing authorization is valid for five years and will then be renewed on the basis of a re-evaluation of the risk benefit balance. Applications for renewal should be submitted at least six months before expiry. Once renewed the marketing authorization will be valid for an unlimited period unless there are justified grounds relating to pharmacovigilance, to proceed with one additional five-year period. Periodic safety update reports (PSURs) will be required in accordance with European requirements. For products with existing national authorizations at the time of implementation of the revised legislation the following will be required:

If acquired via the mutual recognition procedure: one more renewal, following European procedures before the authorization gains unlimited validity. If acquired nationally: a further renewal is not required. This applies to marketing authorizations which have been renewed at least once before 30 October 2005.

In the past the renewal process has sometimes been used to make minor changes to the safety sections of the Summary of Product Characteristics (SmPC). As there will no longer be a continual cycle of five yearly renewals this procedure can no longer be used to update SmPCs and leaflets. Such changes should be notified under the appropriate variation procedure.

USA

Cellular and Gene Therapy[21]

A draft document released in October 2008 by the Food and Drug Administration (FDA) provides guidance to the manufacturers of cellular and gene therapy (CGT) products. This guidance provides recommendations for developing tests to measure the potency of CGT products and provides the requirements for the support of an Investigational New Drug Application (IND) or a Biologics License Application (BLA).

GMP[22]

The FDA has published on 12 November 2008 a Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices concerning equipment validation, control of product containers and closures, production and process controls and the implementation of process analytical technology.

GMP Biological Products[23]

The FDA published on 18 November 2008 the draft guidance for Industry named Process Validation: General Principles and Practices that outlines general principles and approaches that FDA considers to be appropriate elements of process validation for the manufacture of human and animal drug and biological products, including active pharmaceutical ingredients (API or drug substance). The guideline aligns process validation activities with the product lifecycle concepts which are found in existing FDA guidances. This FDA guidance promotes modern manufacturing principles, process improvement, innovation, and sound science that all manufacturers can use in validating a manufacturing process.

References

1. Diário Oficial da União (DOU), *Publication date: 17-Nov-2008*, http://www.in.gov.br
2. Diário Oficial da União (DOU) No 205 of 22-Oct-2008 (Section 1, p.64) *Publication date: 22-Oct-2008*, http://www.in.gov.br
3. Provision KHL-12 Version 2: Requirements for Documents on Good Manufacturing Practice when Submitting Application for Approval/Notification of Clinical Trials, *Oct-2008*
4. Provision VYR-38: Determination of Detailed Requirements for Quality and Safety Assurance in Human Tissues and Cells Intended for Human Use, *18-Oct-2008*
5. Quality Assurance: Good Manufacturing Practice and Inspections
6. http://www.emea.europa.eu
7. Marketing Authorization Procedures: Variations/Changes/Supplements, *Date: Oct-2008*
8. http://www.emea.europa.eu/pdfs/human/press/pr/53947408en.pdf
9. http://www.emea.europa.eu/pdfs/vet/press/pr/52364408en.pdf
10. http://www.emea.europa.eu/pdfs/vet/press/pr/58501208en.pdf
11. http://www.emea.europa.eu/pdfs/human/comp/pr/54030608en.pdf
12. http://www.emea.europa.eu/meetings/conference.htm#
13. www.health.gov.il/
14. The Pharmaceutical Affairs Division of the Health and Hygiene Department of the Prefectural Governments
15. The Pharmaceutical Affairs Division of the Health and Hygiene Department of the Prefectural Governments
16. Regulation No. 436 of 26-Jun-2007: Procedure of Import and Export of

Medicinal Products (Latvian and English Unamended Version)
17. Decree 08.184.1143 of *17-Oct-2008*: Good Manufacturing Practice, http://www.mz.gov.pl
18. Medicines Control Council Web site Publication date: Nov-2008, http://www.mccza.com
19. Resmî Gazete, no 27007, 24/09/2008 *Publication date: 24-Sep-2008*
20. Marketing Authorization Procedures: Renewals
21. Volume 73, Number 197/Pages 59635 – 59636, Docket No. FDA-2008-D-0520, *Publication date: 9-Oct-2008*, http://www.accessdata.fda.gov
22. *Publication date: 12-Nov-2008*, http://www.fda.gov
23. *Publication date: 18-Nov-2008*, http://www.fda.gov

This information was provided by Frank Sayala and Rohini Chari, Pharmaceutical Research Associates (UK).

The Global Information Source for Pharmaceutical Science and Manufacturing Professionals

PHARMACEUTICAL ENGINEERING®

THE OFFICIAL MAGAZINE OF ISPE

JANUARY/FEBRUARY 2009 VOLUME 29, NUMBER 1

Cleaning Validation

Managing Risk

Bacterial Adhesion

Interview with
Senior Staff Members from China's State Food and Drug Administration (SFDA)

ISPE's Science and Technology Initiative

PIC/S-PDA-ISPE Workshop a Success

Good Engineering Practice Guide Released

Official sponsor of: INTERPHEX™

ENGINEERING PHARMACEUTICAL INNOVATION

ISPE

www.ISPE.org

FARR Gold Series® Dust Collectors

Built Like a Safe

TOTAL CONTAINMENT for a safe and healthy work environment.

Gold Series

FARR

Pharmaceutical Dust Applications

- Tablet Presses
- Spray Drying
- Tablet Coating
- Blending
- Fluid Bed Drying
- Granulation

Contained Dust Collection

Safe-change containment systems are available for both the filter cartridges and discharge system underneath the collector. The cartridge change utilizes the bag-in/bag-out (BIBO) method while the discharge uses continuous liner technology.

Call us today **866-530-5474**

www.farrapc.com

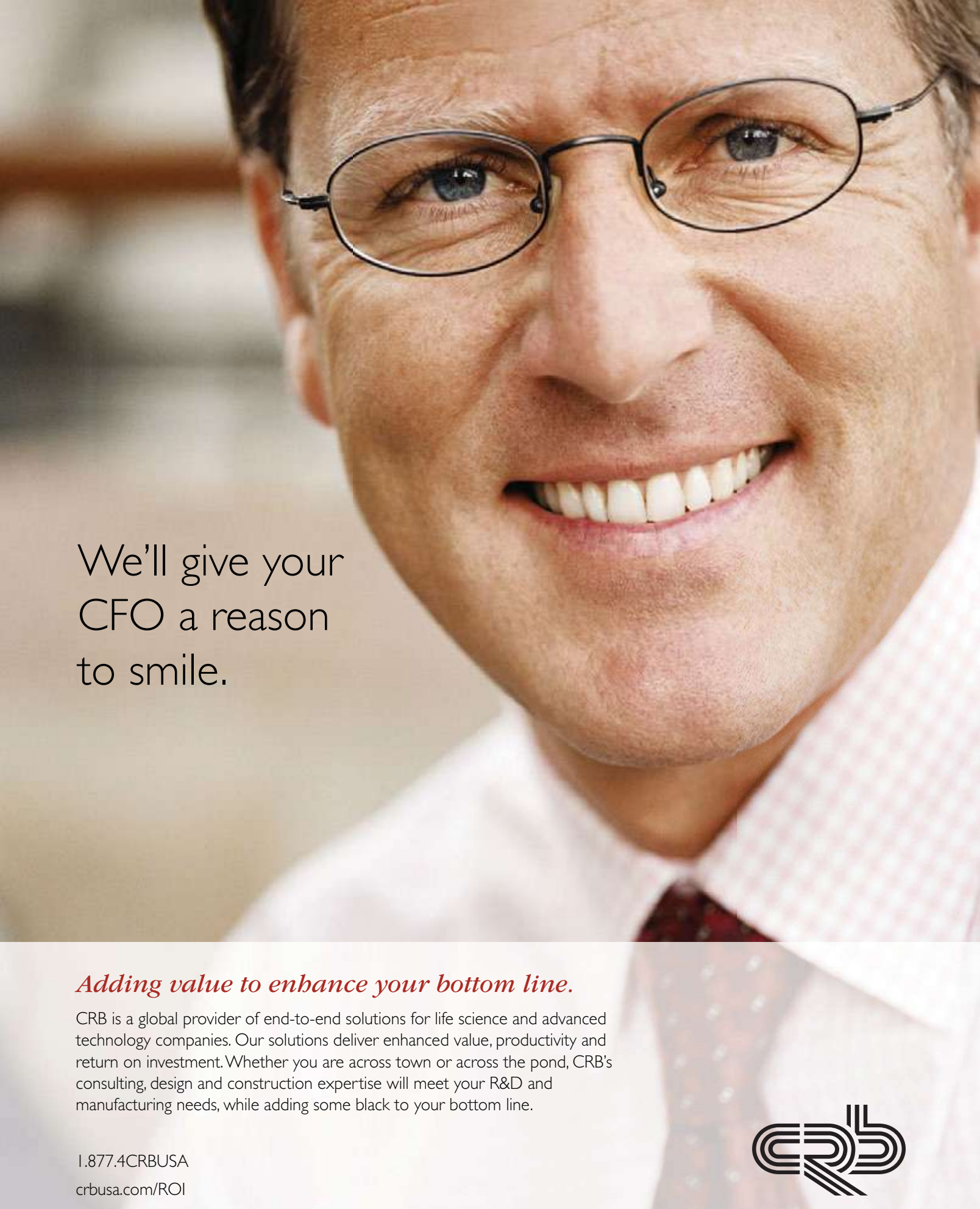
camfil FARR Farr APC is a proud member of the Camfil Farr Group.

Additional APC offices and factories in Laval, Canada (450-629-3030) Manchester, England (44 (0) 1706-238-000) and Kuala Lumpur, Malaysia (6-03-8023-8250)

FARR

Air Pollution Control

870-933-8048 • Jonesboro, AR • email: filterman@farrapc.com



Adding value to enhance your bottom line.

CRB is a global provider of end-to-end solutions for life science and advanced technology companies. Our solutions deliver enhanced value, productivity and return on investment. Whether you are across town or across the pond, CRB's consulting, design and construction expertise will meet your R&D and manufacturing needs, while adding some black to your bottom line.

1.877.4CRBUSA

crbusa.com/ROI

Consulting Design Construction Commissioning Qualifications

The Global Information Source for Pharmaceutical Science and Manufacturing Professionals

PHARMACEUTICAL ENGINEERING®

THE OFFICIAL MAGAZINE OF ISPE

JANUARY/FEBRUARY 2009 VOLUME 29, NUMBER 1

PHARMACEUTICAL ENGINEERING®
(ISSN: 0273-8139) is published bimonthly by ISPE, 3109 W. Dr. Martin Luther King Jr. Blvd., Suite 250, Tampa, Florida 33607, USA. Telephone +1-813-960-2105. Fax +1-813-264-2816. Periodicals postage paid at Tampa, Florida, USA.

BPA

Subscriptions.
An annual subscription to PHARMACEUTICAL ENGINEERING is included in the membership of ISPE.

US Postmaster:
send change of address to Pharmaceutical Engineering, 3109 W. Dr. Martin Luther King Jr. Blvd., Suite 250, Tampa, Florida 33607.

Canada Postmaster:
send change of address information and blocks of undeliverable copies to PO Box 1051, Fort Erie, ON L2A 6C7. Canada Post Agreement Number 40041350.

ISPE HEADQUARTERS
3109 W. Dr. Martin Luther King Jr. Blvd.
Suite 250
Tampa, Florida 33607 USA
Tel +1-813-960-2105
Fax +1-813-264-2816

ISPE ASIA PACIFIC OFFICE
73 Bukit Timah Road
#04-01 Rex House
Singapore 229832
Tel +65-6496-5502
Fax +65-6336-6449

ISPE CHINA OFFICE
Suite 2302, Wise Logic International Center
No. 66 North Shan Xi Road
Shanghai 200041, China
Tel +86-21-5116-0265
Fax +86-21-5116-0260

ISPE EUROPEAN OFFICE
Avenue de Tervueren, 300
1150 Brussels, Belgium
Tel +32-2-743-4422
Fax +32-2-743-1550

www.ISPE.org

PARSONS

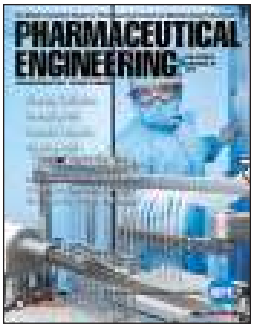
Integrated Solutions for the Global Life Sciences Industry

Engineering, Architecture, Procurement,
Program and Construction Management, Validation

Visit our Booth #1529 at INTERPHEX NYC 2009

www.parsons.com 1.800.555.0532 LifeSciences@parsons.com

Table of Contents



The Global Information Source for Pharmaceutical Science and Manufacturing Professionals

PHARMACEUTICAL ENGINEERING®

THE OFFICIAL MAGAZINE OF ISPE

JANUARY/FEBRUARY 2009 VOLUME 29, NUMBER 1

Cover Photo

Courtesy of Robert Bosch GmbH, Packaging Technology, Crailsheim/ Germany.

Current Issue/Theme

JANUARY/FEBRUARY 2009
Innovative Technology

Next Issue/Theme

MARCH/APRIL 2009
Automation Solutions/ PAT/Operational Excellence

Publishes 23 March 2009

Articles

8 **Online Total Organic Carbon (TOC) as a Process Analytical Technology for Cleaning Validation Risk Management**
by Keith Bader, John Hyde, Peter Watler, and Amber Lane

22 **Using Visible Residue Limits for Cleaning**
by Richard J. Forsyth

36 **Industry Interview Series: Senior Staff Members from China's State Food and Drug Administration (SFDA)**
by Robert P. Best, Robert W. Tribe, Paul N. D'Eramo, and Cheryl Siow

42 **Beyond the Bell Curve: A Report on Managing Capital Project Risk**
by Jeff Lukowski and Mark Bridgers

56 **Fundamentals of Bacterial Adhesion Applied Toward Infection Prevention: Focus on Two Case Studies**
by Yatao Liu, Paola A. Pinzon-Arango, Joshua Strauss, and Terri A. Camesano

Departments

72 ISPE Update
76 Classified Advertising
79 Advertiser's Index

Online Exclusive Articles

Global Regulatory News

For additional information on the pharmaceutical industry in China, including a breakdown of the field, trends, and major issues facing the profession, visit:

visit www.ISPE.org/PharmaceuticalEngineering

ISPE
ENGINEERING PHARMACEUTICAL INNOVATION

Give Feedback via the PAT COP Discussion Forum

The Process Analytical Technology (PAT) COP acknowledges the valuable contribution that Members provide to the Society for technical innovation and industry advancement. We encourage any Member with interest in providing feedback and additional viewpoints to the *Letter to the Editor* to post a message to the PAT COP Web site under the Community Discussions forum. You begin discussions by:

- Logging onto the PAT COP Web site main page: http://cop.ispe.org/COP/PATCOP/
- Click *Create New Topic* on Community Site
- Type your discussion into the *Message* box and indicate *Subject* line
- Click *Post Message* to post discussion

To become a member of the PAT COP and to begin participating immediately, simply go to www.ISPE.org/cops and click the button to the right labeled "Login to COPs" if you are not currently logged in. Otherwise, you will then be taken to the COP Home Page. There, you can choose the "Join/Unjoin COP" tab under the page heading, click the box next to the PAT COP, and then click Join.

23 October 2008

I am writing to you with reference to an article in the September/October 2008 edition of *Pharmaceutical Engineering*. The article was titled "How to Make a Perforated Pan PAT-Compliant" and the banner at the top of the pages of this article read "PAT Compliance." The reason for my letter is to point out that, whilst the technical content of the article was excellent, the phrase "PAT Compliance" is an oxymoron. The whole purpose of the new approach to the management and regulation of pharmaceutical quality, which has been evolving over the past five to six years, has been to move us away from a compliance mentality to one of science and risk management.

So one does not and cannot "comply" with PAT. The PAT approach (which most opinion leaders are now calling the 'Quality by Design (QbD)' approach, as this is the more encompassing term) is about the pharmaceutical industry catching up most other industries in its thinking on quality management. The QbD philosophy is all about utilising scientific knowledge, which is often gained by using PAT techniques to continuously measure the performance of processes in real-time, and risk management to identify the critical to quality attributes of the product and the critical process control points. One of the fundamentals of the QbD approach is that we move away from the era of blind compliance to rules to a position where we think about what we do and have the freedom and responsibility to manage quality in a manner that, firstly, protects patients but also improves efficiency.

So the repeated use of the phrase "PAT Compliance" within this article is unhelpful and misleading in the context of the paradigm shift that the pharmaceutical industry is living through. I would respectfully suggest that the term to use would have been "PAT Capable."

Peter H. Gough
Partner
David Begg Associates (DBA)
York, United Kingdom

This article offers an alternative method to cleaning validation using online total organic carbon analyzers to determine cleaning validation in-situ. Methods are compared with traditional laboratory analysis.

Online Total Organic Carbon (TOC) as a Process Analytical Technology for Cleaning Validation Risk Management

by Keith Bader, John Hyde, Peter Watler, and Amber Lane

Online Total Organic Carbon (TOC) analysis has progressed significantly in the past few years, yet it remains an under-utilized technology. The US FDA has stated that TOC is an acceptable method for both cleaning validation and routine monitoring, provided the suitability of the method has been established and documented.[1] Advances in TOC analyzer oxidation and analysis methodologies make their integration into Clean-in-Place (CIP) systems instrumentation relatively easy as a means to provide near real time cleaning process performance information. While it is currently possible and practical to utilize online TOC analysis for the real-time assessment of CIP cycle performance, the biopharmaceutical manufacturing industry has been slow to adopt it without favorable and accepted regulatory precedents. However, these precedents do exist in FDA guidance documents on Process Analytical Technology (PAT), the Risk-Based Manufacture of Pharmaceutical Products (both in 2004), and the International Conference on Harmonization (ICH) Quality Risk Management guideline in 2005, which signal a regulatory environment receptive to active monitoring and control of critical process parameters.

The case study presented in this article was conducted to test the relative cleanability of three different bottom mounted agitators. The data by which the cleaning process was evaluated was acquired using an online TOC analyzer integrated into the return line of a CIP system as well as by conventional manual indirect and direct sampling and offline analysis.

Implementing TOC as an online process analytical technology requires first determining if the analytical technology and method are appropriate for the application. Primarily, the installation of process analyzers on equipment used in GMP manufacturing facilities should be done only after risk analyses are performed to ensure that the installation does not adversely affect the process or product quality. The location, physical integration, and automation of the online analyzer into the cleaning system return piping are important considerations as these factors may impact the accuracy and robustness of the measurements. Once installed, the reliability of the technology must be demonstrated through a comparison of online results with existing conventional test methods, including any developmental studies supporting the efficacy and appropriateness of the particular analytical method. In this case, the analytical method TOC, is used to detect process and product residues in final rinse water following cleaning.

Selection of a TOC Analyzer Based on Instrumental Characteristics and CIP Process Considerations

The selection of an appropriate TOC analyzer requires knowledge of its basic operating principles to ensure that CIP process conditions do not interfere with analytical results. Since there is little opportunity to customize the available features of an online TOC analyzer, selection of an analyzer with the appropriate oxidation and sensor equipment can accommodate both analyzer specifications and CIP operational requirements. Though the basic operational principles for all TOC analyzers are much the same, the oxidation and sensor technologies vary between manufacturers. Matching the character-

Continued on page 10.

Innovation
makes it possible

Telstar Life Science solutions is constantly innovating to offer tailor-made solutions in high technology equipment for the pharmaceutical, biotech and related industries.

With over 45 years of experience and an international presence in more than 100 countries, Telstar is your partner to provide solutions in the following technologies:

Telstar ACE

High Containment Isolators

Telstar Celester

Sterilization Systems, WFI & Pharmaceutical Steam Generation Systems

Telstar Lyo

Freeze Drying Systems

Containment Systems
- Isolators
- Restricted Access Barrier Systems (RABS)
- Downflow booths

Sterilization Systems
- Moist heat sterilization autoclaves
- Chemical agent sterilization autoclaves
- Sterilization and depyrogenation ovens

WFI & Pharmaceutical Steam Generation Systems
- Multiple/simple effects stills
- Pure steam generators

Freeze Drying Systems
- GMP production freeze dryers
- Laboratory freeze dryers
- Loading & unloading systems

Laminar Air Flow Systems
- Laminar flow benches
- Biosafety cabinets
- Laminar flow booths
- Customized cabinets

Drying Systems
- Hot air drying
- Vacuum drying

Telstar®
Life Science solutions

TELSTAR LIFE SCIENCES
Josep Tapioles 120
08226 Terrassa (Spain)
T. +34 937 361 600
F. +34 937 859 342
sales.pharma@telstar.eu

TELSTAR NORTH AMERICA
1504 Grundy's Lane,
Bristol, PA 19007 (USA)
T. +1 215 826 0770
F. +1 215 826 0222
telstar.na@telstar.eu

www.telstar-lifesciences.com

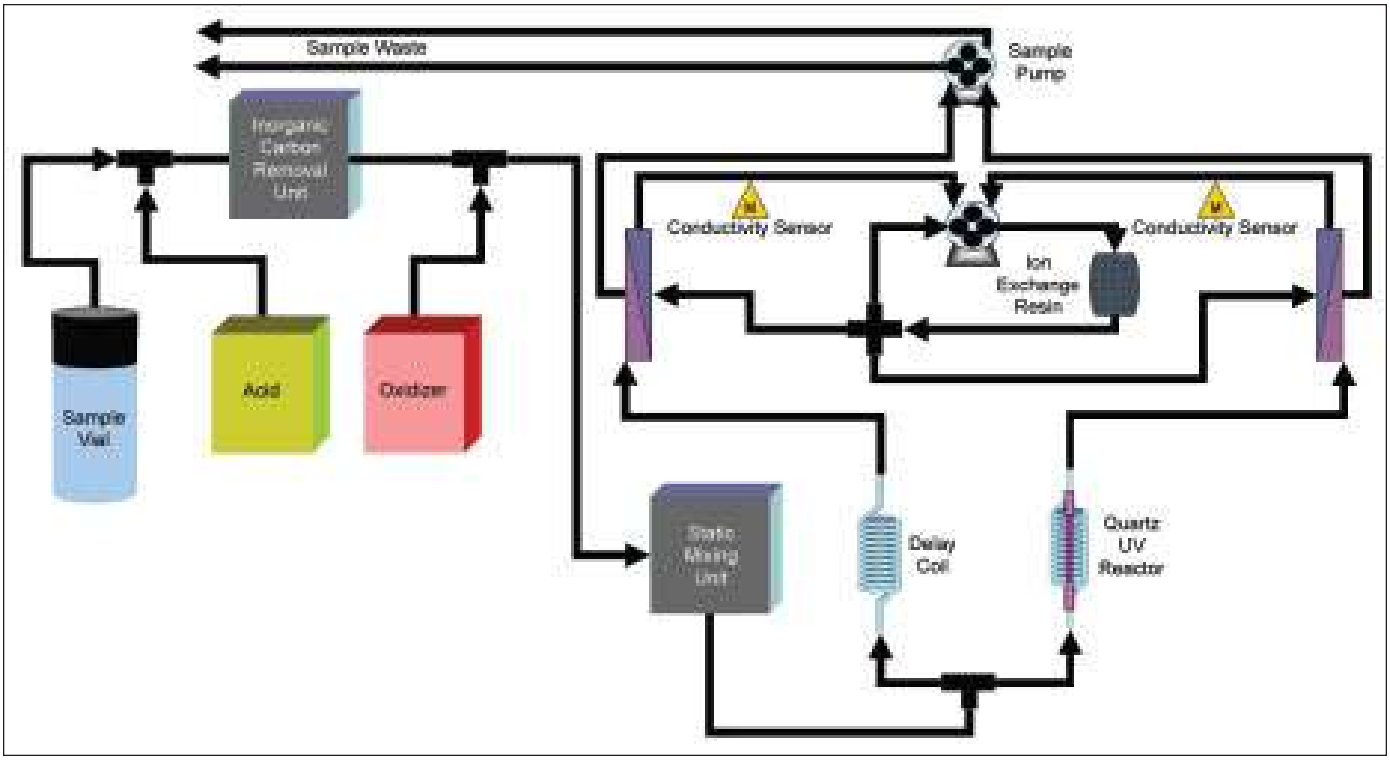


Figure 1. Diagram of a membrane conductometric UV/persulfate TOC analyzer - optional inorganic carbon removal units may be employed if samples have higher levels of dissolved atmospheric CO_2.

istics of CIP processes with an array of specific sensor and oxidation technologies compatible with those characteristics will yield a robust application of the online analyzer, enabling minimized operational and validation efforts with respect to cleaning processes.

For CIP applications, accurate results from an online analyzer must not be confounded by interference from ionic species, variations in sample pressure, or changes in sample temperature. Since conductivity is used in some cases to quantify evolved CO_2, the ionic species in many cleaning agent formulations must be considered as a potential source of interference. These conductive species may be addressed through the use of a membrane conductometric sensor as in Figure 1 or through the use of photometric detection schemes that are insensitive to the presence of conductive ions. Membrane conductometric detectors allow selective permeability of CO_2 across a membrane without permitting other conductive ions into the measurement zone. Therefore, measured conductivity results entirely from Inorganic Carbon (IC) or Total Carbon (TC) oxidized to CO_2, effectively eliminating this source of interference.

For online TOC analyzers in which samples are directly introduced to the analyzer from the CIP return manifold, sample temperature and pressure are relevant parameters to consider. Sufficient pressure is required in the sample line to ensure that the analyzed sample concentration doesn't significantly lag in the CIP return piping. Additionally, care also should be taken to protect the analyzer from pressures exceeding manufacturer's recommendations. In most cases, CIP pressures will not exceed the pressure specifications for an instrument; however, close attention must still be given to the configuration, size, and placement of automated sampling valves and associated sample lines drawing from CIP system return lines. Stabilization of analyzer inlet pressure and flowrate will allow for consistency in the residence time of fluid in the sample lines.

Temperature fluctuations are a relevant concern depending on the selected analyzer, especially if the analysis method is conductometric. Conductivity is a temperature dependant measurement that each instrument manufacturer accommodates in a different manner. Temperature variations in the sample stream may be addressed through temperature compensated conductivity sensors, or measurement of raw conductivity data with sampling apparatus that allow for temperature equilibration through ambient dissipation or active heat exchange. Alternatively, a detection method that is not temperature dependant (such as NDIR) may be used.

TOC concentration is indirectly obtained by calculating the difference between two directly measured parameters; TC and IC. Equation 1 illustrates this relationship.

$$TOC = TC - IC \qquad \text{(Eq1)}$$

Total Carbon is determined by oxidizing organic carbon containing compounds to CO_2 and quantifying both the inorganic carbon already present in the sample along with the evolved CO_2. In the case of a membrane conductometric analyzer (Figure 1), Inorganic Carbon (IC) in analyzed samples results from dissolved CO_2 species (HCO_3^-, CO_3^{-2}), and may be measured directly without oxidation of the sample.

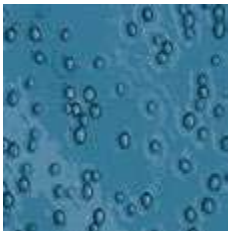
As depicted in Figure 1, solution from the sample vial is injected into the analyzer where acid is introduced to the

Continued on page 12.

GEA Niro Soavi Laboratory Homogenizer

type PANDA™ 2K 1001L

The PANDA™ NS1001 2K is a bench top unit capable of handling a broad range of applications including cell rupture, particle size reduction and emulsions. The PANDA™ 2K with its small hold-up volume and flow rate is ideal for processing small batches of product with results that are directly scalable through to pilot and production machines operating at up to 5500 l/h.



Before

After

PANDA™ NS1001 2K Specifications and Performance:

- Operating pressure 0 – 1500 bar
- Flow rate up to 12 l/h @ 1500 bar
- Minimum sample volume 200ml
- Maximum product viscosity 2000 cPs (20,000 with optional pressure feed)
- Maximum inlet particle size = 0.5mm
- Optional 2nd stage homogenizing valve
- Suitable for CIP and SIP
- ½" Tri Clamp inlet/outlet connections
- Dimensions – L800mm x W460mm x H420mm
- Weight – 85 kg
- 1.8 kW 3ph/60Hz/ 208, 230 or 460V motor (only utility requirement)
- Optional inverter available to allow 1ph/ 60Hz/200-240V power supply

Engineering Excellence.

Process Engineering

GEA Liquid Processing

GEA Process Engineering Inc. • 9165 Rumsey Road • Columbia MD 21045
Tel: 410 997 8700 • Fax: 410 997 5021
E-mail: info@niroinc.com • Website: www.niroinc.com

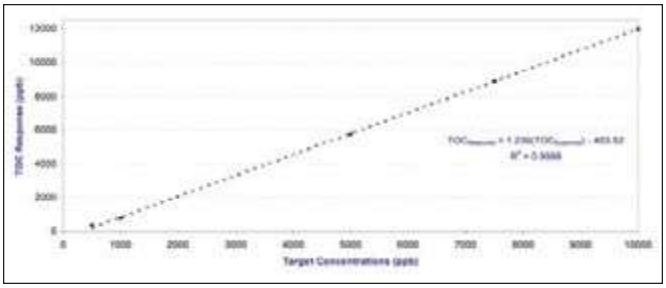


Figure 2. TOC response curve for Bovine Serum Albumin.

sample stream. The added acid shifts the equilibrium such that inorganic carbon species convert to CO_2. After the acid addition, a persulfate oxidant is added and the sample stream mixed to ensure homogeneity. The sample stream is then split with one stream passing through a reactor and exposed to UV light, initiating a photolysis reaction. As the sample in the reactor is oxidized, CO_2 evolves and is transferred across a gas permeable membrane into a deionized water stream where its conductivity is measured. The formation of the conductive species occurs via the carbonate buffer pathway shown in Equation 2.

$$CO_2 + H_2O \leftrightarrow H_2CO_3$$
$$H_2CO_3 + H_2O \leftrightarrow H_3O^+ + HCO_3^- \quad \text{(Eq2)}$$
$$HCO_3^- + H_2O \leftrightarrow H_3O^+ + CO_3^{-2}$$

The other sample stream flows through a hydro-dynamically identical path (identified in Figure 1 as the delay coil) where dissolved CO_2 is transferred across the membrane and conductivity is measured to provide an inorganic carbon reference measurement required for the calculation of TOC.

Analytical and Sampling Method Development

For this study, two analyzers were employed; both equipped with membrane conductometric sensors. The offline analyzer used a methodology based upon UV and persulfate oxidation, whereas the online analyzer used only UV oxidation. To ensure the reliability and comparability of the measurements from the online and offline analyzers, USP system suitability tests were preformed to confirm response efficiency using 1,4 benzoquinone and sucrose standards. The instrumental limit of detection of 50 ppb TOC required per the USP[2] was met for both analyzers.

Once operation of both analyzers was demonstrated to be acceptable, methods were developed using the offline analyzer to characterize the Bovine Serum Albumin (BSA) to be used as a representative process soil and to evaluate and quantify the systemic and experimental error associated with TOC surface swab sampling. Stainless steel coupons also were spiked at multiple weight loadings to develop a recovery response curve.

From a 10% by weight solution of BSA, a series of dilutions were prepared with target concentrations of 500, 1000, 5000, 7500, and 10,000 ppb TOC. The solutions were then analyzed to ensure that the TOC response curve for BSA was linear and to empirically characterize the samples' carbon content to establish a correlation between the concentrations of TOC and BSA.

Analysis of the samples produced the response curve shown in Figure 2. Also reported are the linear regression trend line through the data points, which provides an indication of the linearity of the relationship, Limits of Detection (LOD) and Limits of Quantitation (LOQ). The regression line correlation coefficient (R^2) of 0.9998 demonstrates that the regression line fits the data and is a reasonable model for the plotted data.

To ascertain the surface swab recovery characteristics for BSA, a study was conducted using stainless steel coupons spiked with known concentrations of BSA. The target organic carbon loading (ppb) is indicated by the Sample ID numbers in Table A. To account for the inter-individual variability, the study was conducted with three technicians independently executing the swab sampling method. Swab sampling recovery was evaluated by comparing the TOC recovered from the coupons to the TOC content of positive control samples in which equivalent amounts of BSA solution to that spiked on the surface of the corresponding coupons was spiked into a vial containing 40mL of diluent. The results are summarized in Table A, and shown graphically in Figure 3 and Figure 4.

The correlation coefficient (R^2) value greater than 0.99 for each of the technicians provides assurance that the recovery fits a linear model when inter-individual variability is taken into account. Evaluation of the LOD and LOQ for the sampling method for each technician is shown in Table A and ranges from 122 to 195 ppb TOC, and 371 to 589 ppb TOC, respectively. The slope of each recovery curve also is a representation of the overall surface swab recovery over the

Sampling Technician	Sample ID	Positive Control TOC (ppb)	Blank Corrected Sample TOC (ppb)	Percent Recovery	Sampler LOD	Sampler LOQ
1	250	231	181	78.5	125	377
	500	633	594	93.8		
	1000	1137	1016	89.3		
2	250	231	194	84.1	122	371
	500	633	561	88.5		
	1000	1137	936	82.3		
3	250	280	193	68.8	195	589
	500	808	649	80.2		
	1000	1105	1017	92.0		

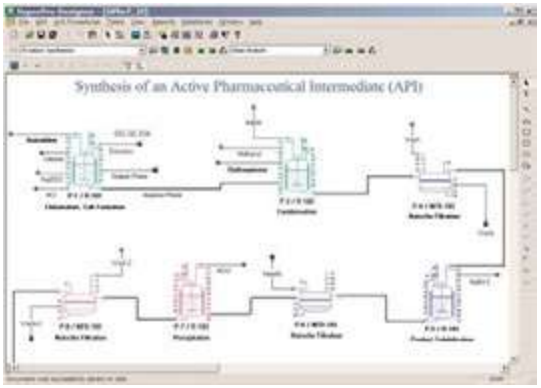
Table A. Surface swab recovery results.

Continued on page 14.

Intelligen Suite

The Market-Leading Engineering Suite for Modeling, Evaluation, Scheduling, and Debottlenecking of Single & Multi-Product Facilities

SuperPro

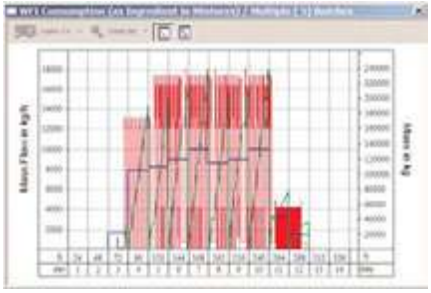


Use SuperPro Designer to model, evaluate, and debottleneck batch and continuous processes

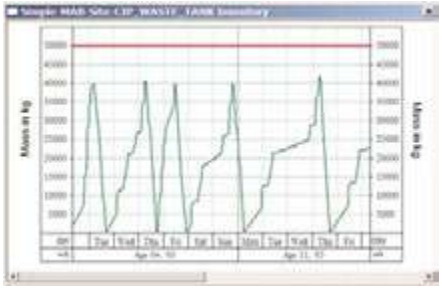
SchedulePro

Switch to SchedulePro to schedule, model, and debottleneck multi-product facilities

Tracking of equipment occupancy in multi-product facilities



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



Inventory tracking for raw materials, intermediates, products, and wastes

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of biochemical, specialty chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 400 companies and 500 universities around the world (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

SchedulePro is a versatile finite capacity scheduling tool that generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of facilities, equipment, resources and work areas. 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 utilities for batch plants, identify equipment requirements, reduce cycle times, and debottleneck facilities.

Visit our website to download detailed product literature and functional evaluation versions of our tools

INTELLIGEN, INC. • 2326 Morse Avenue • Scotch Plains, NJ 07076 • USA
Tel: (908) 654-0088 • Fax: (908) 654-3866
Email: info@intelligen.com • Website: www.intelligen.com
Intelligen also has offices in Europe and representatives in countries around the world

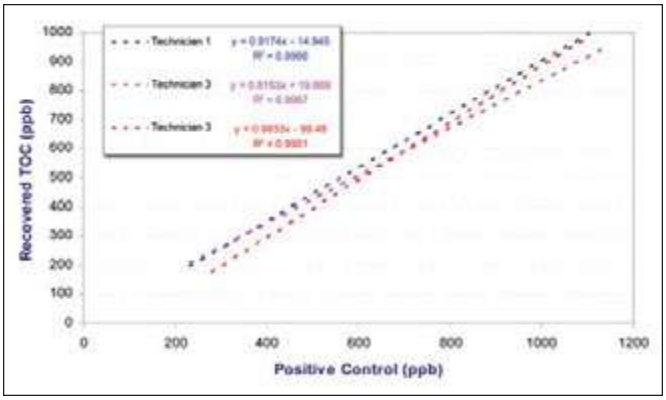


Figure 3. Individual technician swab recovery results.

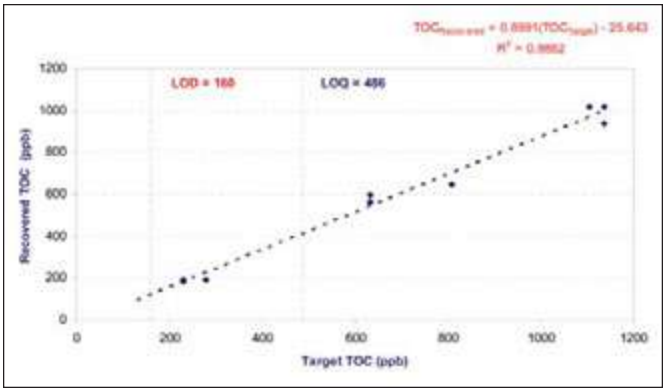


Figure 4. Characterization of TOC surface swab sampling method (BSA swab recovery [aggregate]).

Sampling Method	LOD(ppb TOC)	LOQ(ppb TOC)
Swab	161	486

Table B. Sampling method limits.

range of the indication that on average, each of the technicians will, at a minimum, likely recover greater than 80% of BSA residues remaining on process surfaces within the tested range.

The slope of each line shown in Figure 3 indicates the overall recovery across several residue loadings for each technician. Additionally, relative standard deviation of the individual recovery results was used as the primary statistic of interest to assess the precision of the results and the reliability of the data for each individual technician. Reviewing the discrete relative standard deviation numbers and the R^2 values for each technician, some variability is expected and was apparent.

Intuitively, pooling the data for all of the technicians should create a model incorporating inherent systemic error as well as that resulting from inter-individual variability. To confirm this hypothesis, a t-test conducted for the three data sets confirms that the sample sets for all the technicians may be pooled since they are statistically similar with a high probability of sharing the same sample mean.

Linear regression statistics for the response curve, as well as LOD and LOQ were determined. The LOD and LOQ are evaluated through the following equations:

$$LOD = \frac{3.3s}{m} \quad \text{(Eq3)}$$

$$LOQ = \frac{10s}{m} \quad \text{(Eq4)}$$

In Equations 3 and 4 above, ***s*** defines the standard deviation from the calibration curve and ***m*** the slope of the regression line.[3] However, the quantity, ***s***, may be determined multiple ways: from the standard deviation of the regression line, the standard deviation of y-intercepts of the regression line, and the standard deviation of an appropriate number of blank responses.

The pooled data for all the technicians is represented graphically in Figure 4, and shows an overall recovery of approximately 90% with a correlation coefficient of 0.986, and aggregate limits of detection and quantitation of 160 and 486 ppb TOC.

As noted above, an alternative method for estimating the LOD is to use the average of the swab results from the swabbing of 10 clean stainless steel coupons. This will quantify the approximate background levels resulting from the water, vials, swabs, and other random experimental sources. The average TOC from the swabbing of 10 clean stainless steel coupons was 161 ppb with a relative standard deviation of 9.3%. Accordingly, the LOD values determined by the two methods were nearly identical.

Using TOC swab LOQ as the limit for passing cleaning results, values in excess the TOC swab LOD were evaluated to determine a root cause for the failure. Corroboration of the online and offline rinse samples also was considered in the analysis.

Cleaning Study Results

The CIP test system depicted in Figure 5 was used to compare the cleanability of three bottom mounted agitators of differing design. The components that comprise the CIP test system include a water supply tank, a heat exchanger, automated valves, Variable Frequency Drive (VFD) controlled pumps,

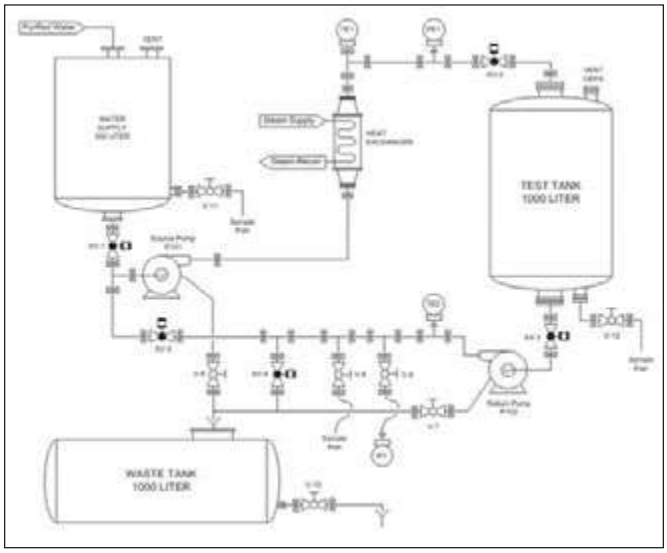


Figure 5. Schematic of CIP skid with online TOC analyzer.

Continued on page 16.

Sharing the value of our combined expertise

Today Edwards Pharmaceutical Systems is part of IMA Group

The best in freeze-drying technology, hand-in-hand with the world's leading name in one stop aseptic processing and filling solutions for the pharmaceutical industry.

At IMA, we are dedicated to building strong client relationships and strive to offer solutions which guarantee efficiency and competitiveness in the global pharmaceutical market.

That is why we have fully integrated Edwards's lyophilisation systems and expertise in order to supply the pharmaceutical industry with even more advanced and complete aseptic processing and filling lines.

IMA LIFE S.r.l.
mktg.filling@ima.it • www.ima.it
IMA EDWARDS
sales@imaedwards.com - services@imaedwards.com • www.imaedwards.com

IMA EDWARDS
Freeze Drying Solutions

IMA LIFE SOLUTIONS: VIAL LOADING • WASHING • DEPYROGENATING • FILLING • FREEZE-DRYING • STOPPERING • CAPPING

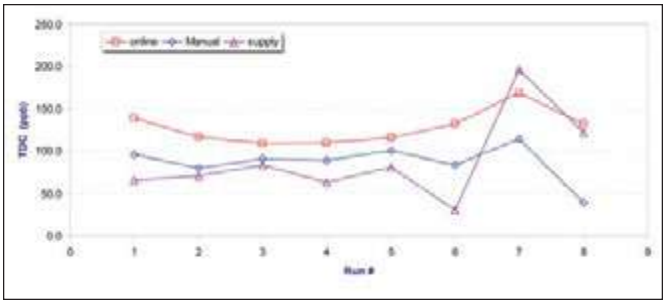


Figure 6. Comparison of manual and online TOC rinse samples.

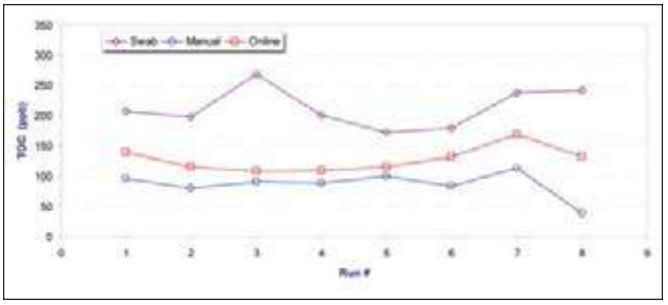


Figure 7. Comparison of online to direct and indirect sampling method results.

and a 1000L vessel in which the agitators were installed for testing. The critical parameters of temperature and flow rate were controlled via PID controllers, along with carefully controlled circuit fill volumes and detergent concentrations to ensure uniform reproducible operations for each run.

To asses each run, final rinse water samples were taken online through the TOC analyzer sample line located at valve V-8. The TOC analyzer is represented in the drawing as analog input signal AI-1. All manual samples taken for comparison were drawn from valve V-9, which was located immediately adjacent to the TOC analyzer sample line. To provide a point of reference for each run, the supply water was manually sampled from V-11. The agitators were each installed in the tank in analogous positions and, as noted before, subjected to the same cleaning procedure and parameters.

To soil the equipment, BSA was manually applied to the internal tank surfaces as well as the entirety of each agitator and allowed to dry. Once dry, the CIP cycle was initiated, consisting of an initial rinse, an alkaline wash, an intermediate rinse, an acidified wash, and purified water final rinses. For each cycle, Steris CIP-100, at 1% concentration by volume, was the cleaning agent used for the alkaline wash. The cleaning agent used for the acidic wash solution was 1% by weight phosphoric acid. The acid wash cycle was then followed by a once-through rinse and a subsequent recirculated rinse. Since the online analyzer required a brief equilibration period before it was ready to sample, the second final rinse was recirculated as once-through rinse durations were inadequate for the analyzer to complete its start up cycle.

Just before completion of the cleaning cycle, manual samples were taken at the beginning of the final rinse recirculation. After completion of the cleaning cycle, manually acquired rinse and swab samples were taken for comparison with those from the online TOC analyzer.

Comparability of the sampling and analytical methods was assessed through analysis of the manual and the online results. These data are shown in Figure 6. The online results also were compared to TOC surface swab samples to any correlation between the methods.

Correlation of the results of all three methods is apparent with the most notable event being the results from run 7. The supply water was accidentally contaminated by overfilling the flat topped supply tank, transferring contaminants from the lid and seal of the vessel into the bulk solution. In each case, the sampling methods detected the excursion.

The comparative results for the surface swab samples are shown in Figure 7. The general trend is the same for the surface swab samples with the exception of run 3 in which the surface swab results are higher than either the manual or online rinse samples. This may have been due to inadequate surface cleaning of BSA residue that was not completely soluble in the final rinse water.

The data from all runs demonstrates that rinse samples, whether online or manual, do provide a good indication of the residue levels on the equipment surfaces with the absolute TOC value difference between swab and rinse samples being attributed to the added TOC background inherent to the swabbing method.

Another interesting observation is the fact that the manually collected rinse sample TOC results were lower than those from the online analyzer, while one might expect quite the opposite. The manual samples were taken at the beginning of the recirculated rinse cycle prior to an extended recirculation time. Once the analyzer had completed the initial rinse cycle (approximately 4 ½ minutes), the online samples were taken. The higher results from online TOC samples may be due to the recirculation of the rinse water prior to sampling. Recirculation of final rinse water is a deviation from typical CIP processes, and recirculation causes the rinse water to be directed back through pathways that would not ordinarily have contact with a final once-through rinse. This potentially contributed some TOC to the final rinse results from the additional surface area contacted by the final rinse water.

Another contributing factor to the higher online TOC results is the configuration of the online analyzer sampling piping which is depicted in Figure 8. The illustration approximates the spatial layout of the sampling equipment. The TOC analyzer sample valve, XV-8, was oriented downward, and did not have an additional drain or flush valve to remove solution from the lines. The manual rinse sampling valve, on the other hand, was flushed prior to sample collection per the procedure for the sampling method, clearing any residue from the sample path that could contribute to elevated TOC levels.

This principle of rinsing the path prior to sample collection and analysis may be incorporated into the sampling arrangement for the analyzer to allow for clearance of residues prior to sample collection. An example of a possible piping configuration to minimize process residue retention is shown in Figure 9. In this arrangement, the sample line branches from the process line such that the inlet to the line is constantly

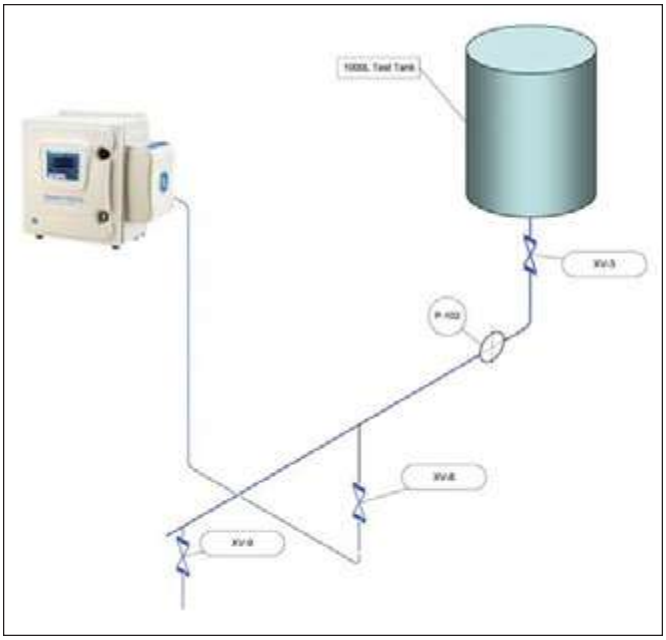


Figure 8. Isometric layout of sampling equipment.

swept clear by the process fluid. Further, the installation of a drain valve is useful to allow for flushing of the line prior to sampling, as well as draining the sample line after sampling is completed. Sloping the sample line back to the drain valve also will minimize retention of process fluid from previous sampling operations.

Conclusions

The cleaning of pharmaceutical manufacturing equipment systems by automated Clean-in-Place (CIP) means has long provided superior reliability and consistency as compared to manual cleaning operations that are subject to human error. Through the introduction of more reliable and affordable sensor technologies, including advances in online TOC technology, the cleaning process can be very effectively controlled and monitored by removing variability inherent to manual collection and analysis of cleaning verification and validation samples. Accordingly, implementation of TOC as a process analytical technology for cleaning systems can improve knowledge and control of the cleaning process beyond real time

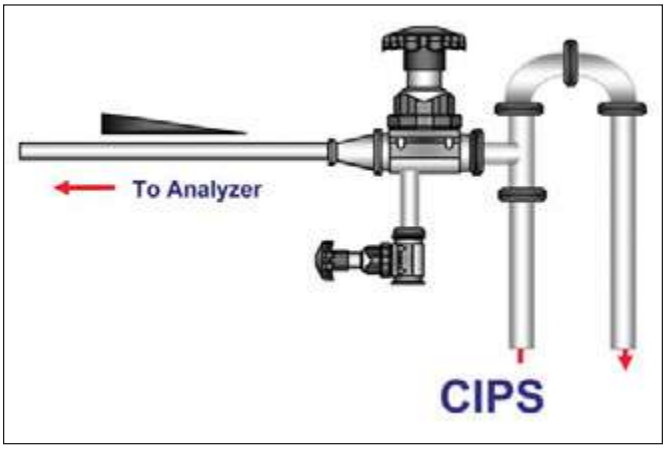


Figure 9. Online analyzer sampling configuration.

Continued on page 18.

awareness of final rinse water quality at a discrete moment in time. The combination of online TOC and online conductivity measurements provides a means for real-time verification of cleaning cycle performance, and using statistical process control methodologies, ongoing analysis of the consistency of critical control parameters and quality attributes for the cleaning process. This ongoing monitoring can provide the basis for evaluating drift and the need for re-qualification based upon events rather than elapsed time. The data from ongoing monitoring also can provide a foundation for cleaning validation that is not based upon a model of three passing commercial scale runs, but rather a model that uses evidence from cleaning cycle performance, on an every run basis, to provide assurance of successful operations prior to the manufacture of each production run.

The implementation of online TOC sampling and analysis must be done by carefully selecting an analyzer that is compatible with the cleaning process and subsequently installing it such that the results are truly representative of TOC levels in final rinse streams. The selected TOC analyzer must be able to tolerate conductive ions such as those present in cleaning agents. The analyzer also must be able to tolerate, and depending on the intended use, analyze occasional spikes of TOC greater than 1 – 2 ppm. This study has demonstrated that an advanced oxidation differential conductivity membrane sensor based instrument is suitable for online CIP rinse water analysis. Other technologies may be suitable based on the specific requirements of the application. If the analyzer will not be used for an application in which conductive ions are present and TOC concentrations are rarely in excess of 2 ppm, it may be possible to use an advanced oxidation based instrument that measures TOC through the use of direct conductivity. For concentrations of TOC in excess of 2 ppm with the possibility of conductive ions, end users may wish to consider the use of a UV persulfate oxidation system with an NDIR or differential membrane conductivity sensor.

Additionally, the sample equipment on the CIP system should be configured to deliver solution to the analyzer quickly without carryover from run to run. This is best accomplished by ensuring a short residence time with adequate turbulence in fully drainable sample lines for complete removal of fluid when the equipment is not in use. Once qualified, the TOC analyzer can identify trends predictive of adverse events or inadequate process control, allowing for timely application of corrective measures. This utilization of real time cleaning process performance information will yield product quality and economic benefits.

To gain regulatory acceptance for the utilization of online TOC analysis for ongoing monitoring of cleaning efficacy, the instrumentation and method must be qualified in a manner consistent with offline validated and compendial sampling and analytical methods. Further, implementation of online TOC sampling and analysis as a component of a PAT strategy for cleaning processes is only practical if the results are equivalent or better than those attained from existing methods. This may be done by comparing the results obtained using both methods and modifying the sampling equipment configuration to ensure that the online methodology is accurate and robust, and at the very least, equivalent to the results of offline sampling methods.

Although some have suggested that online TOC measurement provides additional liability should TOC levels exceed acceptance limits in final rinse water, online TOC measurement compliments and enhances the level of process knowledge from which critical process decisions may be made. Typically, once a system has been validated, TOC rinse samples are not taken for every run unless necessitated by poor system performance or a philosophy that embraces an extremely low risk tolerance. CIP systems often rely on monitoring and control of critical process control parameters, measured by temperature, flow rate, and conductivity sensors in the appropriate locations[12] to ensure that cleaning cycles operate within established and validated ranges. While this approach effectively takes care of the input side of the cleaning process, final rinse water TOC, which is a critical quality attribute for cleaning, has not typically been addressed. Online final rinse water and TOC data will provide more complete information from which to assess the efficacy of cleaning operations on an every run basis, yielding comprehensive and ongoing control well beyond the current status quo.

The monitoring and control of critical quality attributes for cleaning operations offer further economic and quality benefits in reduction or elimination of cleaning related OOSs and their associated investigations and resolutions. These cost reductions can be realized not only through more efficient processes that facilitate faster and more flexible production schedules, but also through the minimization of labor hours invested in manual operations required to support systems, through manual sampling and analysis, which cannot provide the same sensor based process control information. In many manufacturing facilities, cleaning validation samples are manually collected and submitted for analysis to Quality Control laboratories, or in some cases to off-site contract analytical laboratories. These activities involve both time and expense for the manufacturer in the form of labor hours for collection of the data, sample collection materials, time and resources of the QC laboratories, and opportunity cost related to delays in manufacturing operations from waiting for analytical results to determine if cleaning processes were successful.

Finally, the economic benefits of online sampling are supported by the time recorded in the execution of this study to conduct the manual sampling and analysis as compared to the time investment required for running the online analyzer during CIP operations. The time required for the collection preparation and analysis of the samples collected for nine cleaning runs was in excess of 80 labor hours. In contrast, the total set up time for the online analyzer was approximately three labor hours. On a per-run basis, preparations for online analysis and sampling required approximately 20 minutes. In comparison, each run required nearly 10 hours of labor for manual sample collection and analysis. Clearly, extrapolating this time savings over the period of a year indicates that

significant savings may be realized, the magnitude of which depends on the particular facility and the number of cleaning operations to be qualified and monitored. Although integrating online TOC measurements into CIP system automation will result in added capital costs, operating costs can be significantly reduced and will likely justify the investment.

Summary

Sophisticated measurement and control strategies have been successfully applied to CIP systems and operations for many years. The utilization of online TOC measurement represents a significant step forward in assurance of product quality and safety through more effective real-time monitoring and control of the cleaning processes. With enhanced quality assurance and reduced cost of goods as driving forces, pharmaceutical manufacturers are automating manufacturing operations to accommodate more complex processes, including more complicated cleaning sequences commensurate with increasingly complex manufacturing equipment configurations and production methodologies. More robust automated systems will provide higher levels of assurance of removal of potential contaminants to acceptable levels. CIP systems can be automated to the point that risk from manual operator actions are eliminated from the process stream, except for manual set-up activities, such as the loading and un-loading of a glass-washer or the starting of a unit operation from a control point.

References

1. US FDA, CDER, "Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance," http://www.fda.gov/cder/guidance/cGMPs/equipment.htm.
2. USP compendial monograph <643>, Total Organic Carbon.
3. Validation of Analytical Procedures: Text and Methodology Q2(R1), International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
4. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Draft Consensus Guideline, Quality Risk Management, Q9," Released for Consultation at Step 2 of the ICH Process on 22 March 2005.
5. Final Report, "Pharmaceutical cGMP for the 21st Century – A Risk-Based Approach," September 2004, http://www.fda.gov./cder/gmp/gmp2004/GMP_finalreport2004.htm.
6. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, "ICH Harmonized Tripartite Guideline, Pharmaceutical Development, Q8," Current Step 4 version dated 10 November 2005.
7. Guidance for Industry, "Development and Use of Risk Minimization Action Plans," March 2005, http://www.fda.

Concludes on page 20.

gov/cder/guidance/6358fnl.htm.
8. Japanese Pharmacopoeial Forum, December 2005, p. 949.
9. Guidance for Industry, "PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance," September 2004, http://www.fda.gov/cder/guidance/6419fnl.htm.
10. Crompton , T. R., **Determination of Organic Compounds in Natural and Treated Waters**, 1st Edition, Taylor and Francis, 29 W. 35th St., New York, NY, 1999, pp. 809-811.
11. Bader, Keith, ASEPCO Mixer Cleaning Study Report, July 26, 2006 http://www.asepco.com/news/.
12. Hyde, John M., Watler, Peter K., and Bader, Keith, "PAT for Pharmaceutical Cleaning," *Control Engineering*, Vol. 54, No. 4, pp. RX1 – RX4, April 2007.

Acknowledgements

The authors gratefully extend their thanks to ASEPCO for their sponsorship of this project and allowing us to share the collected data and to GE Analytical Instruments for the generous loan of online and laboratory TOC analyzers.

About the Authors

Keith Bader is the Director of Technical and Quality Services at Hyde Engineering and Consulting, Inc. As the Director of Technical and Quality Services at Hyde Engineering and Consulting, he is responsible for the implementation of technical and quality documentation and standards for Hyde Engineering and Consulting on a corporate wide basis. Bader also provides high level consultation externally to Hyde Engineering and Consulting's clients in topic areas ranging from strategic quality and validation documentation to design of experiments for supporting studies. He is currently a member of ISPE and American Institute of Chemical Engineers (AIChE), the Parenteral Drug Association (PDA) and has participated with the Society for Bioprocess Professionals (SBP), now a division of ISPE. He holds a BS in chemical engineering from the University of Colorado at Boulder in 1995. He can be reached by email: keith.bader@hyde-ec.com.

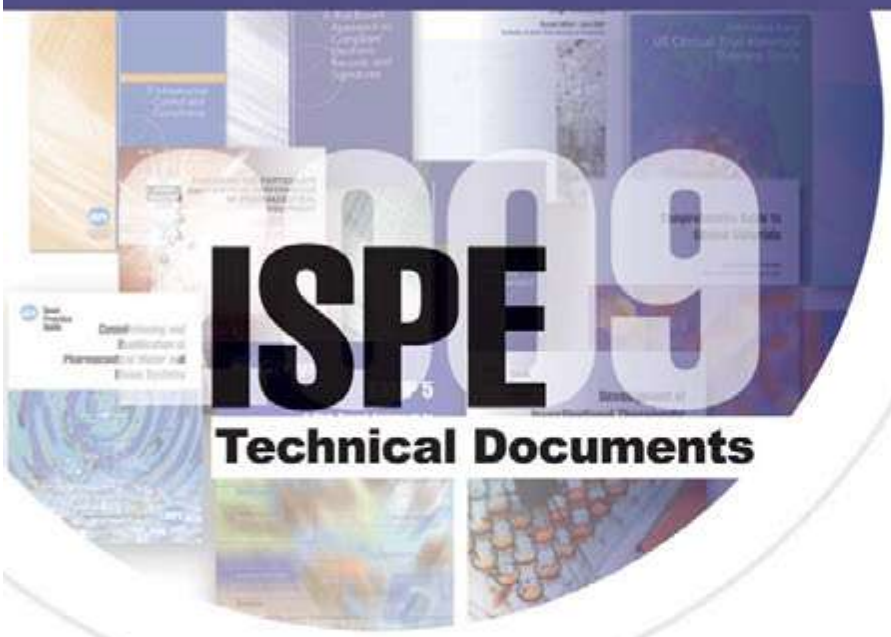
John Hyde is the Founder and CEO of Hyde Engineering and Consulting, Inc., which specializes in providing process engineering, commissioning, validation, and FDA compliance services to biopharmaceutical and pharmaceutical manufacturers. Prior to the formation of Hyde Engineering and Consulting, he was a senior project engineer with Synergen, a biophar-maceutical research and manufacturing company located in Boulder, Colorado. From 1982 to 1992, Hyde was manager, Process Systems Design with Seiberling Associates, Inc., an engineering firm specializing in the design and start-up of pharmaceutical, dairy and food process systems and the application of CIP technology. Hyde serves on the board of the Society of Bioprocess Professionals (SBP) and is a regular speaker at conferences presented by SBP, ISPE, PharmaConference, IVT, Microrite, and other professional societies. He holds a BS in food science and business administration, and a Masters in food engineering, all from Ohio State University. He can be contacted by email: John. Hyde@hyde-ec.com.

Peter Watler, PhD is Principal Consultant and Chief Technology Officer with Hyde Engineering and Consulting, Inc. He has 21 years of GMP biopharmaceutical process experience with a focus on process design and scale-up, facility start-up, and validation. He has prepared three license submissions and participated in several FDA inspections and GMP audits. Watler was previously vice president, manufacturing at VaxGen. He led the design, construction, commissioning, and validation of a GMP facility for vaccine production. He also was responsible for managing supply chain and production operations, led the CMC team, and prepared submissions for government agencies. He previously spent 12 years at Amgen, leading process development, manufacturing support, and overseeing pilot plant operations. He led teams for technology transfer, scale-up, pre-clinical production, and process validation for Neupogen®, Stemgen®, Kepivance®, and Infergen®. Walter holds a BS and an MS in chemical engineering from the University of Toronto and a PhD in Chemical Engineering from Yamaguchi University, Japan.

Hyde Engineering and Consulting, Inc., 6260 Lookout Road, Suite 120, Boulder, Colorado 80301, USA.

Amber Lane is currently the Cleaning Validation Specialist for Insmed Therapeutic Proteins, Boulder, Colorado, where she is responsible for the development and implementation of the companies Cleaning Validation programs. She holds a BA in biology with chemistry from Alverno College, Wisconsin. From 2005-2008 Lane was the analytical services manager for Hyde Engineering and Consulting. In that position, she specialized in analytical studies and the development of analytical methods for cleaning validation. She has nine years of experience with TOC analyzer operation, application, design and development, and validation. Prior to working for Hyde Engineering and Consulting, Lane was the technical trainer with Ionics (now GE Analytical), where she was responsible for the design and implementation of training programs for all products, in addition to playing a role in new instrument development. From 1999-2001, she was an analytical chemist with Abbott Laboratories in Illinois. She is currently a member of the American Chemical Society. She can be contacted by email: alane@insmed.com

Insmed Therapeutic Protiens, 2590 Central Avenue Boulder, Colorado 80301, USA.



Stay on the Cutting Edge with ISPE Technical Documents and Publications

ISPE offers the tools and resources necessary to keep you up-to-date with industry changes, while keeping your production costs low.

ISPE GAMP — Reflecting current regulatory expectations and good practices, the *GAMP® 5* Guide and *GAMP®* Good Practice Guide series help narrow the interpretation of regulatory standards for improved compliance, quality, efficiency, and cost reductions.

ISPE Good Practice Guide — ISPE *Good Practice Guides* (GPGs) provide information on a particular topic area while explaining underlying technical principles and suggest multiple solutions where several outcomes may be possible.

ISPE Baseline® Pharmaceutical Engineering Guide — ISPE's *Baseline® Guides* offer practical answers to challenges facing facility designers while providing an understanding of products and processes.

ISPE GMP Institute — GMP products and publications make good business sense and help meet regulatory requirements.

Electronic licenses are now available.
Contact Gloria Hall at ghall@ispe.org for more information.

ENGINEERING PHARMACEUTICAL INNOVATION ISPE

For more information on these or other ISPE technical documents and publications, visit www.ISPE.org/publications today!

This article presents the use of visible residue limits. Parameters were defined, their ruggedness determined, and applications described.

Using Visible Residue Limits for Cleaning

by Richard J. Forsyth

Introduction

Before formal cleaning validation programs were instituted, visual inspection was the primary means of determining equipment cleanliness. The use of visual inspection is still typically a component of a cleaning validation program and for routine inspections of cleaning effectiveness. The use of only visual examination to determine equipment cleanliness was proposed as far back as 1989 by Mendenhall.[1] He found that visible cleanliness criteria were more rigid than quantitative calculations and clearly adequate. The FDA, in their "Guide to Inspection of Validation of Cleaning Processes," limited the potential acceptability of a visually clean criterion to use between lots of the same product.[2] LeBlanc also explored the role of visual examination as the sole acceptance criterion for cleaning validation.[3]

The Acceptable Residue Limit (ARL) for drug residue is often determined on a health-based and an adulteration-based criterion.[4,5,6] The limit used is the lower of the two limits. A health-based limit is generated from toxicity data, which can be expressed as Acceptable Daily Intake (ADI). The health-based limit is calculated using the ADI or lowest therapeutic dose and the parameters of the equipment used to manufacture the formulation.[5] For the adulteration limit, a carry-over limit of 10 ppm or a baseline limit of 100 µg/swab is often used in the industry.

Our health-based limit calculation is:

$$ADI/MDD \times DUB/SSA \times M = ARL\ (\mu g/swab)$$

Where: ADI is the Allowable Daily Intake (µg/day) of the residue in question which would have no pharmacologic effect; MDD is the Maximum Daily Dose (units/day) of the subsequent product manufactured in the equipment; DUB is the Dose Units per Batch (units) of the subsequent product; SSA was the Shared Surface Area (cm^2) for the product contact surface area of the manufacturing equipment; M is the swab area (cm^2/swab). Our adulteration-based limit is 100µg/swab.[7] An established visible residue limit, which is below the Acceptable Residue Limit, is a reasonable criterion for cleaning validation.

Visible cleanliness is the absence of any visible residue after cleaning, but a number of factors influence any determination. The most obvious is the observer. Not only the observer's visual acuity, but also training on what to observe, influences the outcome of a visual inspection. The levels of illumination in the inspection areas and shadows caused by the equipment influence what is seen. The distance and the angle of the observer from the equipment surface also have an effect. Finally, the individual residues that comprise a given formulation affect the overall visible residue limit. Jenkins and Vanderwielen observed various residues down to 1.0 µg/cm^2 with the aid of a light source.[4] Fourman and Mullen qualitatively determined a visible limit at approximately 100 µg per 2 × 2 in. swab area[8] or about 4µg/cm^2.

Sample preparation and viewing parameters for VRL use have been established for both pilot plant and commercial manufacturing facilities.[9,10] A solution or suspension of the API applied at different concentrations to stainless steel coupons results in residues of uniform size. Multiple observers determined VRL levels under controlled viewing conditions. The VRL was established at the lowest residue concentration all observers visually detected. A study of viewing parameters, including viewing distance, viewing angle, light intensity, residue composition, and observer subjectivity resulted in optimal viewing conditions to detect

Continued on page 24.

Important technological advances are brewing in the biopharmaceutical industry…

…and advanced high-purity solutions from MKS are behind many of them.

MKS Instruments, a global leader in critical process management and control, develops and manufactures a wide range of products used in today's most sensitive biotech and biopharmaceutical processes. From instruments to control pressure and flow, to ozone generators for sterilization, to stainless steel fittings, filter housings and housing heaters, MKS has the expertise and cost-effective solutions to address the needs of the most advanced bio processes. For information on these and other MKS products, visit us online at **www.mksinst.com/biopharm.**

mks
Technology for Productivity

MKS Instruments, Inc. Phone: 978.284.4000 or 800.227.8766 (USA only) www.mksinst.com/biopharm

visible residues. Viewing conditions in the pilot plant were set at 18 inches, 30°, and > 200lux. For commercial facilities with larger, fixed equipment, the viewing inspection parameters are more restricted. The optimal viewing conditions for VRLs are ≤ 10feet, ≥ 30°, and > 200lux. A discussion of the applications of VRL use and the associated risks concluded that the potential for a cleaning failure was small under a well controlled VRL program.[11,12,13]

The subjectivity of the observers and the appearance of the dried residues remained as potential limitations to a VRL program. The original VRL work used a small group of four to six observers.[9,10] For subsequent work, a larger pool of observers determined the VRLs of development APIs at one site. In addition, a study of VRL determinations of five APIs at multiple sites helped serve to address the issue of observer subjectivity as well as further define the ruggedness of residue sample preparation. Observers are qualified with a training program consisting of VRL determinations of compounds with already established VRL levels, while emphasizing the importance of residue appearance and viewing parameters.

Applications of VRL use in pilot plant and manufacturing facilities were described.

Visible Residue Parameters

The variables associated with studying visible residue in the pilot plant were defined, and then experimental parameters for the study were established. The parameters considered were: surface material, light intensity, distance, angle, residue appearance, and observer subjectivity.[9]

Stainless steel was an obvious choice for surface material, since >95% of manufacturing equipment surfaces are stainless steel. Representative stainless steel coupons were used for spotting purposes in the laboratory setting.

The lighting conditions in the manufacturing pilot plant differ from room to room. The light intensity was measured in each room of the pilot plant and ranged from 520 – 1400 lux. To allow for shadows and different positions within a given room, it was decided to conduct the visible residue study between 400 and 1400 lux using a light source directly over the sample. A fluorescent light served as a light source to provide the same type of light that is used in the pilot plant. A plastic cover with different degrees of shading was placed over the bulb and was rotated to adjust and control the intensity of the light. A light meter was used to set and verify the various light intensity levels.

To minimize observer subjectivity, a pool of observers viewed all of the samples. A distance of six to 18 inches from the equipment surface and a viewing angle of zero to 90° were considered as practical viewing parameters. A comfortable viewing distance of 12 inches was chosen. A viewing angle of 30° was chosen although lower angles occasionally provided more reflectance. A 30° angle provided the shallowest practical viewing angle, taking into consideration the surface locations where residues are most likely to be seen in manufacturing equipment, i.e., corners and joints.

The lighting conditions in the commercial manufacturing suites differ from room to room and also depend on equipment size and degree of disassembly for cleaning. The larger size of the equipment in the manufacturing facility provided the greatest difference compared to the smaller equipment in the pilot plant. The increased size deepens the shadows in the interior of the equipment. To compensate for lighting conditions, a portable light is used for inspection as necessary. Therefore, the range of lighting for this study was from 100 lux up to the intensity of the portable light. For the lower lighting level, ambient fluorescent light served as a light source to provide the same type of light used in the manufacturing plant. The portable light source was a hand held light. The portable light source was adjusted to maximize viewing conditions. Moving the light source allowed the observer to control the lighting conditions; i.e., optimize the incident light angle and the effect of reflected light on the formulation residue, and minimize the reflecting light back to the observer. A light meter was used to set and verify the various light intensity levels.

The viewing distances for this study were dependent on the size of the equipment. In a commercial manufacturing facility, equipment sizes are larger and viewing distances are greater. Rather than define viewing distances for each piece of equipment, viewing distances were chosen at five, 10, 15, and 20 feet to complement the pilot plant data.

The viewing angle also is restricted by the equipment size and configuration. Therefore, residues were viewed over a range of angles from 15° to 90°. The minimum angle resulted from a combination of comfortable viewing angle coupled with viewing distance. Intermediate viewing angles of 30° and 45° were evaluated in addition to perpendicular (90° to the observer) viewing.

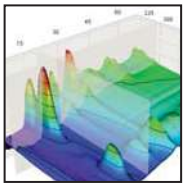
To minimize the effect of observer subjectivity, four subjects viewed all of the samples independently. Sample concentration levels were spotted above and below the previously determined VRL to allow for increased distances and higher intensity light respectively. Therefore, the targeted spotting levels for the formulations were at the swab limit concentration of the API, which is typically 4 µg/cm^2, the previously determined VRL, at the VRL +25% and at the VRL -25%.[10]

Residue appearance varied from white, crystalline to gray. The standard preparation for residue spots involved pipetting 100µl of sample solution or suspension onto the material coupon. This volume of methanol consistently supplied a circular residue spot of about 5 cm in diameter, which was approximately the 25 cm^2 area that was swabbed. As the sample concentrations decreased, the appearance of the residues was less likely to appear as a uniform residue and more likely to appear as a ring. The non-uniform or ring appearance of the residues at the VRL would be observed on equipment after cleaning. As residue levels increase, the VRL would fail a piece of equipment long before it became uniformly coated with residue. A uniformly visible residue would be so far above the VRL, it would indicate a completely ineffective cleaning procedure.

Continued on page 26.

The only complete solution for Process Analytical Technology.

Enable Real-Time Release Through Quality by Design



ABB's Industrial IT for PAT is a globally-supported, end-to-end solution for PAT (Process Analytical Technology) implementation. This system takes full advantage of the FDA's PAT guidance. It supports Quality by Design (QbD) as well as real-time product release initiatives. In addition, it allows online process verification and continuous process improvement. From analyzers and automation to services and support, only ABB stands ready to implement a total PAT solution to keep your plant running smoothly – today!

For more information, visit us at www.abb.com/lifesciences, www.abb.com/analytical or email pharmaceutical.info@us.abb.com.

Power and productivity for a better world™

ABB

Parameter Limitations

As expected, the overall ability to visually detect formulation residue decreased with increased viewing distance[10] - *Figure 1*. At 400 lux and at the minimum viewing angle, observers were able to detect residue at the swab limit concentration, as well as the VRL for all tested formulations from 5 feet. Several of the formulation VRLs were not detected from 10 feet. From 15 feet, the observers were not able to see the majority of the VRLs and were not able to detect any of the VRLs consistently from 20 feet. With regard to the ARLs, the observers saw the majority of the formulation residues under these viewing conditions from 10 and 15 feet[10] - *Figure 2*. From 20 feet, the observers saw less than half of the formulation ARLs.

The ability to detect visible residue also diminished with decreased ambient light[10] - *Figure 3*. With ambient light down to 200 lux, VRLs were consistently detected from 15 feet and a 45° viewing angle. With ambient light at 100 lux, some VRLs were not detected at 15 feet and 45°. However, VRLs were consistently detected from 10 feet at 100 lux.

The ambient light source controlled the light intensity at the lower end of the range. The portable light source controlled the light intensity at the upper end of the range. The observer moved and adjusted the orientation of the portable light source to optimize individual viewing conditions within the constraints encountered in different manufacturing equipment; therefore, the maximum intensity of the portable light source decreased with distance. In general, the use of the spotlight did not increase the observer's ability to detect formulation residue - *Figure 4*.

The viewing angle of the observer to the residue was a critical parameter in the ability to detect the formulation residue. Under ambient light and at the minimum angle, about 15° - *Figure 1*, the observers did not detect the majority of the VRLs at 15 feet and only detected a few at 20 feet. When the viewing angle was increased to 30°, the observers detected more residue spots at both 15 and 20 feet, but not enough to make a significant difference compared to the 15° data. As the viewing angle was increased to 45° and 90°, the observers detected almost all of the VRLs at 15 feet and detected the majority of the VRLs at 20 feet. The observers detected essentially all of the ARLs at 20 feet at viewing angles greater than 30° - *Figure 2*. When the position of the observer was varied with respect to the stainless steel background, observers detected all VRLs from 10 feet at a 45° coupon angle down to 100 lux.

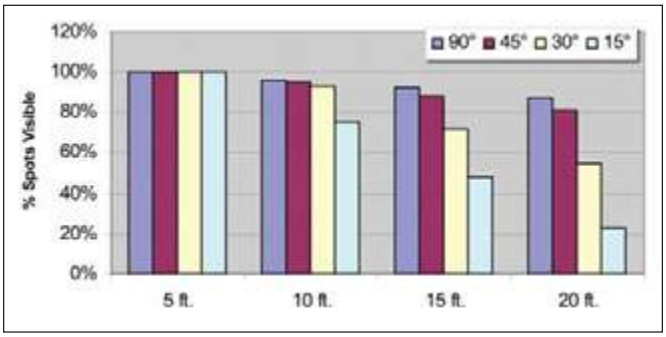


Figure 1. VRL detection versus distance and viewing angle at 400 lux.

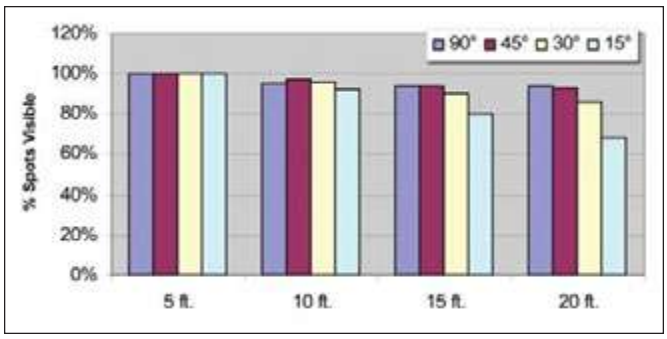


Figure 2. ARL detection versus distance and viewing angle at 400 lux.

Training

Observer variability was a factor in determining the VRL[9] for API and formulation residues. The pool of observers were recruited based on job function, i.e., those performing VRLs, those cleaning the equipment, and those inspecting the equipment. A level of visual acuity is necessary for the various job functions. No additional eye test was required for observers in order to mimic real conditions. The data showed that the observer's ability to see the residues was not a limiting factor to VRL determinations. Each viewing parameter examined had an effect on the observer's ability to detect the formulation residues. Observer detection was dependent on the formulation residue level, observer viewing distance, light intensity, and viewing angle. Certain observers had trouble detecting several of the formulation residues. Observer variability increased with greater viewing distance and became a factor beyond 10 feet. This same trend was seen with the observer angle factor. At the minimum angle of 15° and at 30°, observer variability was comparable to the other parameters. However, at a viewing angle greater than 30°, the ability to detect residue increased significantly and observer variability decreased accordingly - *Figures 1 and 2*. Observer residue detection was comparable using the portable light source and ambient light at 400 lux (Figure 4) and was not a significant factor at decreasing light intensity levels until 100 lux, where detection of VRLs was problematic - *Figure 3*.

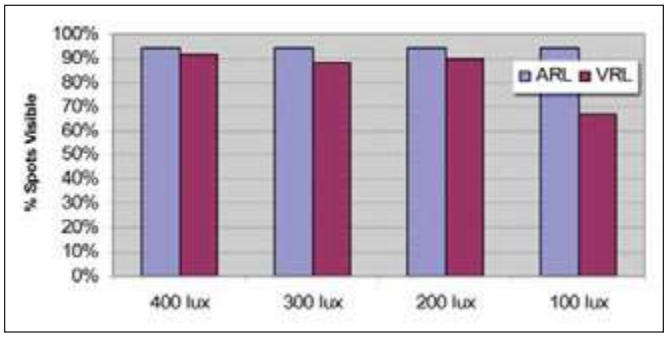


Figure 3. ARL and VRL detection versus decreasing light intensity at 15 ft. and 15°.

Continued on page 28.

A Single Resource...

for TOTAL Cleanroom Confidence.

Planning & executing the right cleanroom solution for your critical process.

AES is your single resource to deliver fast track solutions for Pharma & BIO applications, such as:

- **API Clean Containment**
- **Fill/Finish Processes**
- **Blow/Fill/Seal Facilities**
- **EU/Grade A Laminar Flow Upgrades**
- **Low cost ISO 8/CNC Macro Environments**
- **Cell Manufacturing Facilities**

With the AES Pharma Wall System, combined with our expert knowledge of HVAC and process integration, let us show you how the AES "single resource" team can deliver maximum value to your cleanroom investment.

Call Grant Merrill at 888-237-2532 (ext. 139) to arrange your free consultation today.

VISIT AES AT

Interphex Puerto Rico
Booth 507
Jan. 29 & 30, 2009

Interphex New York
Booth 2928
Mar. 17, 18 & 19, 2009

aes
Clean Technology, Inc.

1-888-AES-CLEAN ext. 139
237-2532

aesclean.com

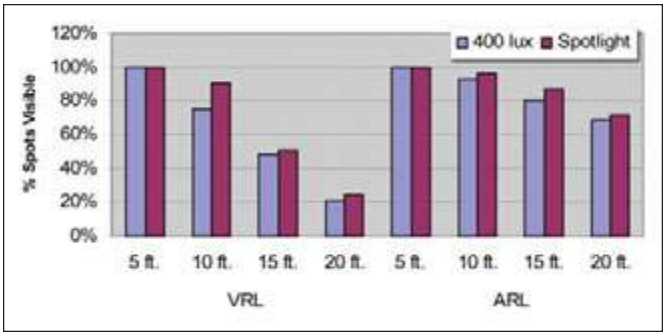


Figure 4. ARL and VRL detection at 400 lux and maximum light intensity at 15 ft. and 15°.

The parameters which influence the ability to detect visible residues were determined and viewing of residues can be controlled. Under defined viewing conditions, a trained observer will be able to visually detect formulation VRLs. The observer should be within 10 feet of the equipment surface. This minimizes the influence of the light intensity or viewing angle. Secondly, the observer should view the surface from multiple angles greater than 30°. This minimizes the possibility of the residue blending in with the background. Finally, the ambient light level should be at least 200 lux. Otherwise a portable light source can be utilized.

VRL Ruggedness

Initial vs. Later VRL Determination

Of the original 59 VRLs established,[9] the average VRL was 1.6µg/cm². Three of the four observers agreed on most residue levels, but one observer differed, which resulted in slightly higher VRLs. Since observer agreement was a condition for the VRL determinations, the individual VRL data points were unaffected by the observer variability. Of the original set of VRLs, 78% were less than 2µg/cm², but 14% were greater than 4µg/cm² - *Table A and Figure 5*. Additional VRL determinations increased the experience level, widened the observer pool, and refined the experimental technique. Instead of a small, dedicated group of observers, the individuals working on the development compound established the VRLs. The observer pool is now between 20 to 30 individuals. However, the most significant difference in the subsequent VRL determinations was the standardization of the residue spot preparations using lower spotted residue levels - *Table B*, which resulted in lower Visible Residue Limits. Interestingly, the variability among the observers decreased even as the observer pool increased. The greater observer consistency was a result of several factors: the initiation of a VRL training program for observers and equipment cleaners and inspectors; the overall increased experience level of the observers and the consistent residue spot preparation technique. Of the additional VRLs established, the average VRL dropped to 0.9 µg/cm² and 89% of the determinations were less than 2µg/cm², 96% of the total were less than 3µg/cm², and only 2% were greater than 4µg/cm² - *Table A*. A t-test comparison of the original and additional VRL data in Figure 5 resulted in a t-stat of 2.45, which is greater than the t-critical value of 1.96 for a two tail comparison with a 95% confidence limit and showed that the data distributions were not equivalent. The additional VRL data with its lower average, were statistically

	Original VRL Data		Subsequent VRL Data	
VRL (µg/cm²)	**Number of Compounds**	**%Total**	**Number of Compounds**	**%Total**
< 1	33	56%	148	76%
1 – 2	13	22%	25	13%
2 – 3	3	5%	14	7%
3 – 4	2	3%	4	2%
> 4	8	14%	3	2%
Total	**59**	**100%**	**194**	**100%**

Table A. Comparison of VRL data.

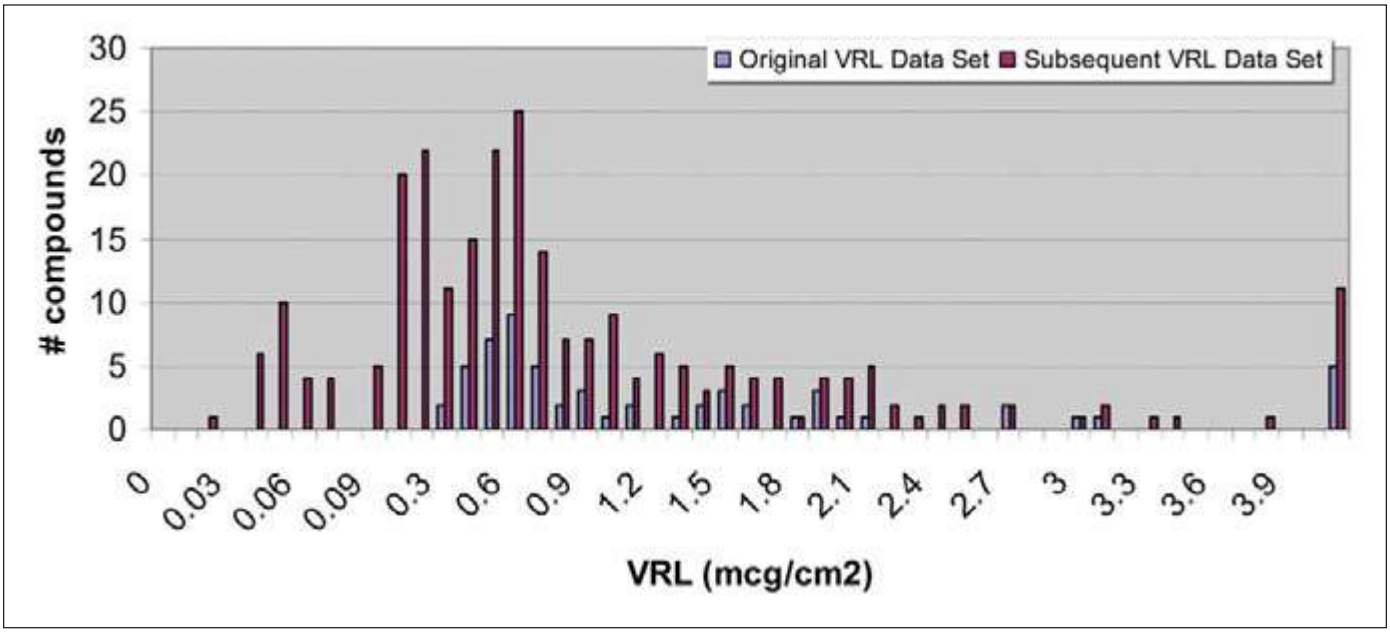


Figure 5. VRL distribution.

Continued on page 30.

Stop wishing. Start saving. The S3℠ System has arrived!

Introducing the S3 System: a revolutionary way to purify water. At Siemens, your wish is our command. Our S3 System significantly lowers your energy and operating costs while lengthening the life of pumps, membranes and other components. Contact your Siemens representative today to learn how the innovative S3 System technology can help make your wishes to reduce operating costs, and to become a "greener" organization, come true.

For more information, call 800.875.7873 ext. 5000 or visit
www.siemens.com/s3

Water Technologies

SIEMENS

Spotting Solution Prep	Residue Spotted	Target Concentration (20 cm^2)
Soln A – 20 mg into 25ml	80 μg	4 $\mu g/cm^2$
Soln B – 5 ml of A into 10 ml	40 μg	2 $\mu g/cm^2$
Soln C – 5 ml of B into 10 ml	20 μg	1 $\mu g/cm^2$
Soln D – 5 ml of C into 10 ml	10 μg	0.5 $\mu g/cm^2$
Soln E – 5 ml of D into 10 ml	5 μg	0.25 $\mu g/cm^2$
Soln F – 1 ml of D into 10 ml	1 μg	0.05 $\mu g/cm^2$
Solvent	0 μg	0 $\mu g/cm^2$

Table B. Residue target concentrations.

VRL ($\mu g/cm^2$)	APIs	Formulations	Excipients	Detergents	Total (%Total)
< 1	76	51	46	8	181 (68%)
1 – 2	18	9	8	3	38 (17%)
2 – 3	10	2	4	1	17 (7%)
3 – 4	3	2	1	0	6 (3%)
> 4	6	0	5	0	11 (5%)
Total	**113**	**64**	**64**	**12**	**253 (100%)**

Table C. Current VRL data.

different when compared to the original VRL data, which confirmed the effects of experience and technique refinement. The overall average VRL is now below 1.1µg/cm^2 for the 253 VRLs determined to date - *Table C* since 63% of the VRLs determined are "less than" the lowest level tested.

API vs. Excipient vs. Formulation Determinations

An analysis was conducted of the VRL data broken down into API, excipients, and formulation categories to determine any VRL correlation between a formulation and its components. Earlier work[9] compared the VRL of 12 formulations against the VRLs of the formulation components. Logically, the VRL of the formulation would be the same as the lowest component VRL. That was the case in seven of the 12 comparisons. However, in three of the cases, the formulation VRL was higher and in the other two, it was lower than the component VRLs.

The more important comparison was between the VRL of the formulation and its API. In the pilot plant, it is not practical to perform a VRL on every development formulation. The formulation compositions continually evolve up to the final market formulation selection. In the VRL comparison of formulations against components,[9] nine of the 12 formulation VRLs were lower than the VRL of the respective API. In one case, they were equal and in the remaining two, the formulation VRL was higher. The data concluded that the VRL of the API is not a good indicator for the VRL of a formulation.

However, the data was generated during the original VRL work, where the residue concentrations and observer variability were higher. The subsequent VRL work generated additional data with increased experience and refined technique. The data gap narrowed between the formulations and APIs. The current average VRL of 64 formulations is 0.7µg/cm^2 and of 113 API determinations is 1.0 µg/cm^2. The average VRL of the 64 excipients tested to date is 1.6 µg/cm^2. The VRL data showed significant overlap among formulations, APIs, and excipients. A t-test comparison of the API and formulation VRL data in Table C and Figure 6 showed that the data distributions were equivalent. The formulation VRL data, despite its lower average value, was not statistically different when compared to the API VRL data. The expanded data set analysis concluded that the VRL of the API was a good indicator for the VRL of a formulation. One can determine the VRL of a development API and safely employ that number as the VRL for the development formulation(s).

Multi-Site Study

The VRL data from the three sites are shown in Table D. Data from the UK site were generally lower than from the other sites. Data from the US site were slightly higher, which correlated to smaller spot sizes and resulting higher spot concentrations.[14] The observers in the UK and US typically were able to detect the lowest or next to lowest residue level. The data from the Canadian site showed three VRLs which were higher than the other sites. Observer variability at Montreal also was greater. Of the three higher levels, one was comparable to the established VRL, while the other two were higher than the established VRL. All three were still well below the adulteration limit of 4µg/cm^2. A review of the observer data showed that in all cases the higher levels were based on one observer not detecting the residue. Otherwise the data more closely agreed with the other sites.

The variability of the multi-site data was the result of several factors. The sample solution concentrations, spot sizes, and the resulting residue concentrations influenced the VRL determination. The UK site's lowest residue level was lower than the other sites, which explained their overall lower VRL levels. The observer variability at the Canadian site was similar to the early US site data. A single observer skewed the results compared to the other observers and other sites.

Two grades of stainless steel finish were evaluated. The majority of process equipment is mill (matte) finish, but the use of mirror (electropolish) finish equipment has increased. There were no consistent differences between the VRL results from the mill and mirror stainless steel finishes. The

Compound	Established VRL ($\mu g/cm^2$)	U.K. VRL ($\mu g/cm^2$)		U.S. VRL ($\mu g/cm^2$)		Canadian VRL($\mu g/cm^2$)	
		Mill	Mirror	Mill	Mirror	Mill	Mirror
A	0.67	< 0.29	< 0.25	< 1.06	< 0.83	2.00	< 0.22
B	0.485	< 0.33	< 0.28	< 0.52	< 0.40	0.64	1.33
C	< 0.36	< 0.26	< 0.53	< 1.12	< 1.12	0.61	< 0.23
D	2.05	< 0.49	< 0.52	< 0.93	< 0.56	2.29	< 0.23
E	< 0.61	< 0.23	< 0.25	< 0.42	< 0.64	2.00	0.47

Table D. Multi-Site VRL data (mill finish and mirror finish stainless steel).

VRL Application	Pilot Plant/Manufacturing	Process Risk	Risk Mitigation
New Compound Introduction	Pilot Plant	**Low** New worst-case	· VRL determination · Redundant inspection · Evaluate API physical properties
New Compound Introduction	Manufacturing	**Low** New worst-case	· Redundant inspection · Evaluate formulation physical properties and cleanability
Routine Use Inspection	Pilot Plant	**None**	· Already in place · Cleaning validation
Routine Use Inspection	Manufacturing	**None**	· Already in place · Cleaning validation
Periodic Assessment	Pilot Plant	**Low** Carryover	· Redundant inspection · Periodic swab confirmation
Periodic Assessment	Manufacturing	**Low** Carryover	· Redundant inspection · Periodic assessments trending performance based on visual inspections.
Technology Transfer	Pilot Plant	**Low**	
New Equipment Introduction	Pilot Plant	**Low** Cleaning procedure doesn't work	· Redundant inspection · Evaluate versus current equipment
Campaign Length Extension	Manufacturing	**Low to None**	
Cleaning Procedure Optimization	Pilot Plant	**None**	· Surface sampling after optimization
Cleaning Procedure Optimization	Manufacturing	**None**	· Surface sampling and validation after optimization
Reduced Cleaning Documentation (Manual Cleaning, Equipment accessible to visual inspection)	Manufacturing	**Low to None**	· Data to demonstrate VRL < ARL · All cleaning parameters demonstrated during validation

Table E. VRL application and risk assessment.

finish of the stainless steel had no impact on the VRL determinations.

It was concluded from the study that VRL determination was comparable at the three sites and the experimental

Continued on page 32.

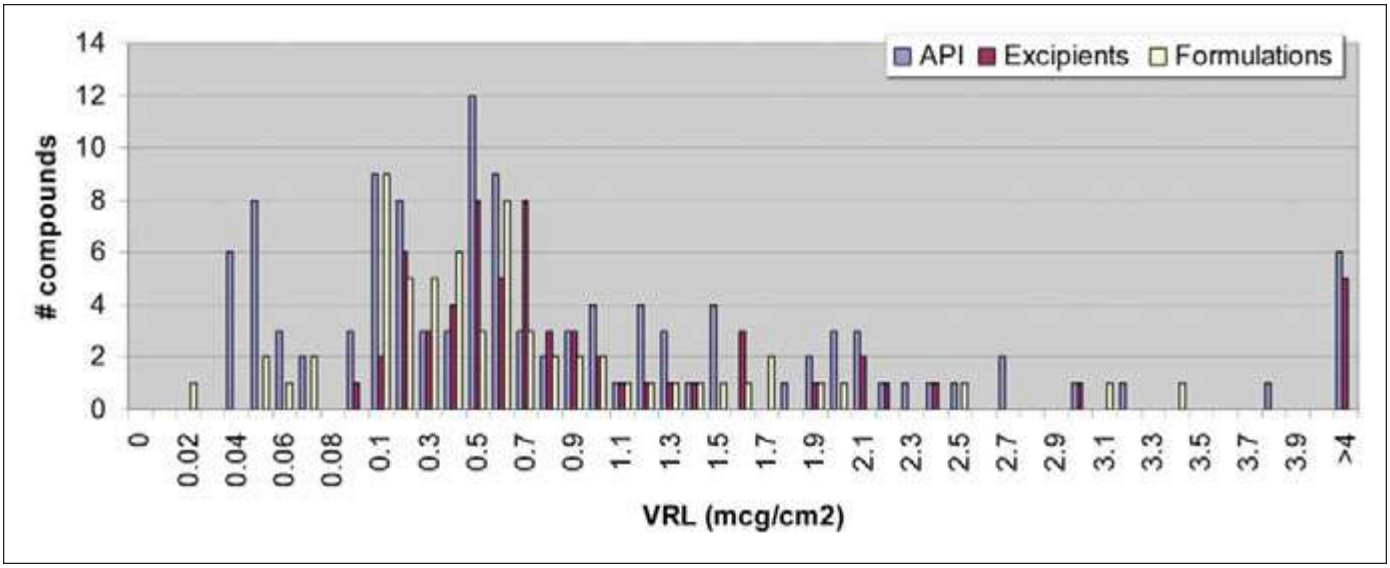


Figure 6. VRL distribution.

variability from sample preparation and observer subjectivity posed no risk for a potential cleaning failure since all VRL values were well below the ARL. The study also pointed out the value of VRL training program and the experience gained through ongoing visual equipment inspections.

Residue Appearance

The standard preparation for residue spots involved pipetting 100µl of sample solution or suspension onto the material coupon. This volume of methanol consistently supplied a circular residue spot of about 5 cm in diameter, which was approximately the 25 cm^2 area that was swabbed. As the sample concentrations decreased, the appearance of the residues changed from a uniform residue to that of a ring - *Figures 7 and 8*.

To determine the effect of spotting volume, 60µl of the lowest spotted solution was pipetted along with 0, 20, 40, 60, 80, and 100 µl of methanol. The lowest concentration was used since the appearance of the residue near the VRL was the primary area of interest. The appearance of the different volumes had little effect on the appearance of the residue around the VRL. All of the residues were similar, but as expected the rings became larger with the increased volume - *Figure 9*. Eventually, larger volumes of spotting solvent would make the ring too dilute to detect, but the area of the ring at that point would be significantly larger than the swab area of 25 cm^2.

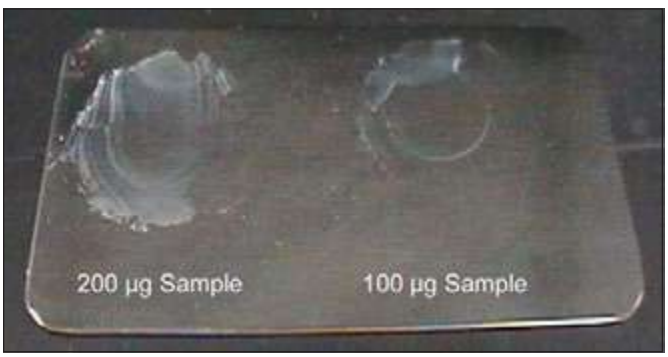


Figure 7. Effect of concentration on residue appearance.

It can be concluded that the appearance of residues near the VRL concentration are expected to take on the appearance of a ring. If the residue has a uniform appearance, it is most likely well above the VRL limit.

Applications

Uses of VRLs by a Pilot Plant Facility

The use of VRLs has previously been described[9,11] for the introduction of new compounds into a pilot plant. Before a new compound is manufactured in the pilot plant, a VRL is established for the API. After the initial batch is manufactured, the equipment is cleaned and visual inspection using the VRL confirms the current cleaning procedure is sufficient and that the new compound is not a new worst-case requiring further validation. This application along with its risk mitigation is shown in Table E.

VRLs also are used for periodic assessment of cleaning in the pilot plant. Monthly independent visual inspections using VRLs are conducted on several pieces of equipment to assure that routine cleaning removes all product residues. Over the course of the year, these independent periodic inspections check all of the different types of equipment in the pilot plant to generate a comprehensive review of ongoing cleaning effectiveness in the pilot plant.

Other uses of VRL in the pilot plant include technology transfer either to a contract or a manufacturing facility. Since cleaning procedures between facilities are different, VRLs would be a quick, simple verification of cleaning in place of analytical method transfer and testing. VRLs also can be used for the introduction of new equipment into the facility. VRLs would be an efficient way to get equipment on line and ensure baseline cleanliness, while demonstrating equivalency with respect to the cleaning efficacy of a previously validated procedure.

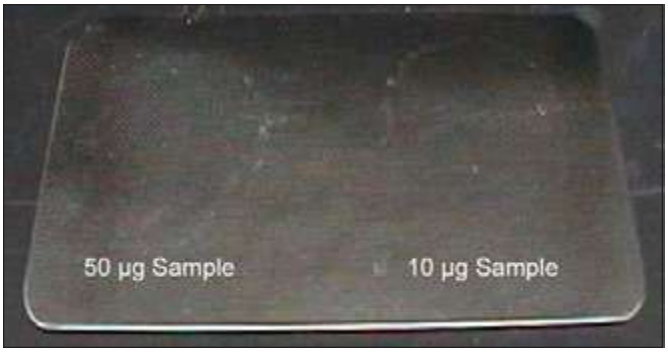


Figure 8. Effect of concentration on residue appearance.

The optimization of new cleaning procedures during development is another application for VRLs. Cleaning cycle times could be challenged with VRL determination as the acceptance criteria. A more immediate benefit would be realized with manual cleaning procedures. Personnel who clean the equipment could effectively determine optimal scrub times and rinse volumes with a visual limit.

Uses of VRLs in a Manufacturing Facility

Several opportunities to apply VRL as a surrogate to surface sampling have been identified in manufacturing facilities using Good Manufacturing Practices (GMPs). Process controls and procedures also have been identified to mitigate the risks when applying VRL in a GMP facility. Given that VRL determinations for drug product formulations have been established[9,10] and the relative accessibility to visual inspections with this equipment, the scope of these applications would be primarily applicable to pharmaceutical manufacturing and primary packaging operations.

As with pilot plant facilities, VRL data may be used to develop new or optimize existing cleaning procedures. The extent of routine documentation and cleaning records could be streamlined in a GMP facility. Once optimal scrub times and rinse volumes have been validated and incorporated into the cleaning procedure, visual cleanliness may be the only critical cleaning parameter that would require documentation on a routine basis. With VRL data, a check by a second person for visual cleanliness confirms performance and ensures that the level of residuals is below the acceptable residue level. This procedure may obviate the need to record actual cleaning parameter data (i.e., scrub times and rinse volumes) on a routine basis and reduce the volume of GMP documentation that must be maintained for marketed drug products.

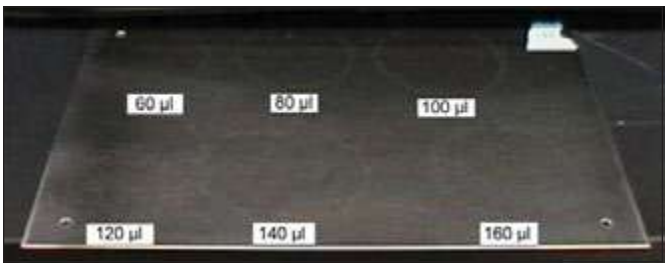


Figure 9. Effect of volume on residue appearance – 6 µg sample.

VRL data and visual inspection may be applied to support the introduction of new products into existing validated product matrices. The use of product matrices or bracketing product residues to validate a "worst case" for multi-product equipment modules is a common practice in industry and supported by regulatory guidance.[2,15-17] If not a new worst-case, the VRL of the new compound can be compared to the validated ARL. If the new compound is less than the ARL, visual inspection alone should be satisfactory for revalidation of the cleaning procedure for a new product.

The interval of use (manufacturing campaign) and the interval between end of use and cleaning are process parameters that must be validated. For stable products manufactured in freely draining equipment, there should be low-to-no process risks with respect to extending a validated campaign length based on visual inspection. Routine inspections for visual cleanliness would mitigate any potential process risks with carryover of process residuals and confirm cleaning performance. The risks for bioburden proliferation are low due to the absence of water and moisture. This same rationale could be applied to extending validated times for the interval between the end of use and equipment cleaning.

Once a cleaning process is validated in a GMP manufacturing environment, the process should be monitored periodically to ensure consistent and robust performance. Independent visual inspections should be incorporated into the peri-

Concludes on page 34.

odic assessment program to confirm that the cleaning processes remain in a state of control. A second person should check for visual cleanliness and the frequency of recleaning is an appropriate metric for assessing cleaning performance. This additional control helps to ensure robustness of the validated cleaning procedure. With an appropriate VRL program, visual inspection may be used rather than surface or reinstate testing to demonstrate continued consistent cleaning performance.

Conclusion

Visible Residue Limits (VRLs) have been evaluated for pilot plants and manufacturing facilities from a risk-assessment perspective. The VRL data, particularly when compared to the health-based cleaning limit for most compounds, makes VRL use a low risk approach to cleaning verification and validation. The ruggedness of VRL viewing conditions has been tested and optimal viewing conditions defined. The current studies established the ruggedness of VRL determination among multiple observers at different sites, showed the relationship between VRLs of formulations and individual components, and assessed the effects of residue appearance on VRL preparation parameters. The studies also highlighted the value of a VRL training program for all personnel involved in the program. Opportunities for VRL implementation have been identified along with the acceptable mitigation of the associated risks.

References

1. Mendenhall, D.W., "Cleaning Validation," Drug Development and Industrial Pharmacy, Vol. 15, No. 13, 1989, pp. 2105-2114.
2. FDA, "Guide to Inspection of Validation of Cleaning Processes," (Division of Field Investigations, Office of Regional Operations, Office of Regulatory Affairs, July 1993).
3. LeBlanc, D.A., " 'Visually Clean' as a Sole Acceptance Criteria for Cleaning Validation Protocols," PDA J .Pharm. Sci. and Technol., Vol. 56, No. 1, 2002, pp. 31-36.
4. Jenkins, K.M. and Vanderwielen, A.J., "Cleaning Validation: An Overall Perspective," Pharm. Technol., Vol. 18, No. 4, 1994, pp.60-73.
5. Forsyth, R.J. and Haynes, D., "Cleaning Validation in a Pharmaceutical Research Facility," Pharm. Technol., Vol. 22, No. 9, 1998, pp.104-112.
6. LeBlanc, D.A., Danforth, D.D., and Smith, J.M., "Cleaning Technology for Pharmaceutical Manufacturing," Pharm. Technol., Vol. 17, No. 10, 1993, pp. 118-124.
7. Forsyth, R.J., Leblanc, A., Voaden, M., "A Single Adulteration Limit for Cleaning Validation in a Pharmaceutical Pilot Plant Environment", Pharm. Technol., Vol. 31, No. 1 2007, pp. 74-83.
8. Fourman, G.L. and Mullen, M.V., "Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations," Pharm. Technol., Vol. 17, No. 4, 1993, pp. 54-60.
9. Forsyth, R.J. and Van Nostrand, V., "Visible Residue Limit for Cleaning Validation and its Potential Application in a Pharmaceutical Research Facility," Pharm. Technol., Vol. 28 No. 10, 2004, pp. 58-72.
10. Forsyth, R.J. and Van Nostrand, V., "Application of Visible Residue Limit for Cleaning Validation in a Pharmaceutical Manufacturing Facility," Pharm. Technol., Vol. 29, No. 10, 2005, pp. 152-161.
11. Forsyth, R.J. and Van Nostrand, V., "The Use of Visible Residue Limit for Introduction of New Compounds in a Pharmaceutical Research Facility," Pharm. Technol., Vol. 29, No. 4, 2005, pp. 134-140.
12. Forsyth, R.J., Hartman, J.L., and Van Nostrand, V., "Risk-Management Assessment of Visible Residue Limits in Cleaning Validation," Pharm. Technol., Vol. 31. No. 4, 2007, pp. 134-140.
13. Forsyth, R.J., Lukievics, T., Roberts, J., and Van Nostrand, V., "Correlation of Visible Residue Limits with Swab Results for Cleaning Validation," Pharm. Technol., Vol.30, No. 11, 2006, pp. 90-100.
14. Forsyth, R.J., et al, Internal Report: Multi-Site Study for Visible Residue Limit Determination in the Solid Dosage Pilot Plants, 22 January 2008.
15. EudraLex, Annex 15, "Qualification and Validation."
16. Pharmaceutical Inspection Co-operation Scheme (PIC/S), "Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-sterile Process Validation, Cleaning Validation.
17. Health Canada , Health Products and Food Branch Inspectorate, "Cleaning Validation Guidelines."

About the Author

Richard Forsyth is an Associate Director with GMP Quality at Merck & Co., Inc. He is responsible for internal and external facility audits, as well as document audits for regulatory submissions. He has worked in Quality for three years and prior to that worked as an analytical chemist in Pharmaceutical R&D for 23 years. He has been involved with cleaning validation for more than 15 years. Forsyth has a broad range of GMP/GLP analytical experience, including methods development and validation as well as formulation development and project management. He is an adjunct Professor in the QA/RA graduate program at Temple University. Academic training includes an MS in chemistry and an MBA in management, both from St. Joseph's University in Philadelphia, Pennsylvania, USA. He can be contacted by telephone: +1-215-652-7462 or by email: richard_forsyth@merck.com.

Merck & Co., Inc, Worldwide GMP Quality, WP53C-307, West Point, Pennsylvania, 19486, USA.

Get industry know-how from the convenience of a computer.

ISPE Online Learning

Part of ISPE's family of Online Learning tools, these programs offer basic to intermediate knowledge on key topics and serve as an excellent primer for ISPE classroom training and conference seminars. Many relate to the seven Certified Pharmaceutical Industry Professional™ (CPIP™) certification program knowledge areas of product development, facilities and equipment, information systems, supply chain management, production systems, regulatory compliance, and quality systems. Select programs that match your needs at **www.ISPE.org/onlinelearning**.

Available Recorded Webinars

- Airflow Pattern Visualization
- Clinical Trials: A Primer
- Enabling On-Demand: A Practical Alternative to the Traditional Method of Packaging and Labeling of Clinical Supplies
- Equipping SMEs to Perform Effective Training
- Good Training Practices! Improving Compliance and Performance with Effective Training
- Introduction and Update on ISPE's New *Risk-MaPP Baseline® Guide* (Complimentary)
- Manufacturing of Potent Drugs - An Industry Perspective on Facility Design, Measurements and Controls, as Presented to the FDA
- Overcoming Regulatory and Logistical Hurdles When Conducting Clinical Trials in India
- Risk Management in a Regulatory Context: Overview and Examples
- Top Five Critical Issues Facing the PAT Professional

Online Webinars for CPIP™ Certification Program Preparation

Product Development

- Formulation, Clinical Phases, and Manufacture
- Technology Transfer
- Production Scale-up and Optimization

Facilities and Equipment

- Design and Construction/Installation
- Commissioning and Qualification as a Risk Management Strategy
- Operation and Maintenance
- Controls and Automation

Information Systems

- Information Systems

Supply Chain Management

- Materials Management
- Operational Economics (Coming Soon)
- Warehouse and Distribution Management

Production Systems

- Production Unit Operations (Drug (Small Molecule); Biologics) (Coming Soon)
- Production Management
- Production Control

Regulatory Compliance

- Government Regulations (Coming Soon)
- Standards, Practices, and Guides

Quality Systems

- Risk Management and Quality Management Systems
- Systems Validation

ENGINEERING PHARMACEUTICAL INNOVATION ISPE

www.ISPE.org/onlinelearning

In this interview, senior staff members from China's State Food and Drug Administration share the latest developments and achievements of China's activities in drug manufacturing and supervision of drug safety, and ideas for future potential cooperation with ISPE and other international organizations in the industry.

PHARMACEUTICAL ENGINEERING Interviews

Senior Staff Members from China's State Food and Drug Administration (SFDA)

by Robert P. Best, Robert W. Tribe, Paul N. D'Eramo, and Cheryl Siow

Editor's Note: In light of the burgeoning pharmaceutical industry in Asia, ISPE's involvement with activities in this region is growing rapidly, especially in China. Last year, ISPE made several monumental strides to build a presence in a country that continues to increase its role on the world stage.

In 2008, ISPE opened an office in Shanghai; recruited close to 30 local volunteers who are forming ISPE's first China Affiliate; started ISPE's first Student Chapter with more than 100 members at Sichuan University; and joined forces with the China Center for Pharmaceutical International Exchange (CCPIE) to bring education programs to Chinese pharmaceutical professionals at the ISPE China Conference in November in Beijing.

Moving into 2009, there will be more activity to come. Pharmaceutical companies will increasingly rely on China for integrated research, development, and innovative manufacturing solutions. The Chinese pharmaceutical government and industry are aware that to move beyond imitation toward innovation, they must have an educated workforce trained in the latest technologies and informed about the latest global regulations.

As a neutral organization that promotes worldwide collaboration to improve the industry on a scientific and technical basis, ISPE met with senior staff members from China's State Food and Drug Administration (SFDA) in November in Beijing to share ideas and information.

In addition, Robert P. Best, President and CEO, ISPE, Robert W. Tribe, ISPE Asia-Pacific Regulatory Affairs Advisor, Paul N. D'Eramo, Executive Director, Johnson & Johnson, Global Quality, ISPE Past Chairman, and Cheryl Siow, Manager, ISPE China Office, conducted an interview with the following SFDA officials on behalf of *Pharmaceutical Engineering*:

- JiangYing Yan, Spokeswoman of SFDA, Deputy Director-General, Department of Policy and Regulations, SFDA
- WenZuo Chang, Counsel, Department of International Cooperation, SFDA
- JianHua Ding, Director, Division of Pharmaceuticals, Department of Drug Registration
- Ai Liu, Consultant of Liaison Division, Department of International Cooperation, SFDA
- QingWu Guo, Deputy Director, Division of Drug Manufacturing Supervision, Department of Drug Safety and Inspection, SFDA
- Zhongzhi Qian, Professor, Director, Division of TCMs Standard, Chinese Pharmacopoeia Commission
- Lili Cao, Director, Division of External Cooperation, CCPIE, SFDA

More comprehensive information on the current state of China's pharmaceutical industry is available in the Country Profile on China, a Supplement included with this issue of *Pharmaceutical Engineering*.

• • •

JiangYing Yan We know that *Pharmaceutical Engineering* is a world-renowned publication of ISPE. We hope to share with the world the latest developments and achievements of China's activities in drug manufacturing and supervision of drug safety and the future potential cooperation.

Continued on page 38.

In commissioning, validation and compliance, teamwork and timing are everything.

COMMISSIONING AGENTS. We're in position, skillfully negotiating every turn to help you get to your project's finish line faster and more efficiently. Our teams undergo a rigorous program of structured training, qualification, and continuous professional development. You'll find we aren't selling individual resumes, we're selling a high performance team.

For every project, teamwork and timing are everything.

- **Commissioning planning and field execution**
- **Validation planning, protocol development and execution**
- **Process validation, cleaning, sterilization and computer validation**
- **Process improvement services: Process Analytical Technology (PAT), technology transfer and process studies**
- **Technical services including design reviews, SOP development, maintenance programs and training**
- **cGMP compliance audits and regulatory reviews, compliance improvement projects, comparability protocols and other submission assistance**

CAI Commissioning Agents, Inc.

WWW.COMMISSIONINGAGENTS.COM

Achieve world class manufacturing.

Call Robert E. Chew, P.E., Vice President
Robert.Chew@CAgents.com
+1.317.710.1530

"ICH played a very important role in China's regulatory system. We adopted many guidelines from ICH in drafting our local technical guidelines."

Q What is the status of the revised China GMPs?

QingWu Guo I would like to briefly introduce the process of the revision work on the China GMPs which will help you understand our work. We started revising GMP Revision 98 four years ago. We conducted a study on all the available GMP guidelines in the world for two years. The study covers the GMPs of the Australian Therapeutic Goods Administration (TGA), the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S); the European Medicines Agency (EMEA); the World Health Organization (WHO); the US Food and Drug Administration (FDA); and the Japanese Ministry of Health, Labour and Welfare (MHLW). We began to revise the current GMPs after the study and comparison. The first draft of the GMP has been completed and we will post it on the SFDA Web site to solicit opinions at the end of this year or early next year. If you have a chance to look at the draft, you will find the new revision of the GMPs is quite similar to what the EMEA and the WHO have, but some of the format has been tailor-made for China. We welcome ISPE's suggestions and opinions on the draft.

I would like to address that we included a detailed appendix on Traditional Chinese Medicines (TCMs). It might be different from other countries since TCMs have many kinds of formulations, including sterile and non-sterile. According to the specialties of TCMs, we set up detailed regulations, especially for the process of the pretreatment, which is not required in other countries. China has Good Agricultural Practices (GAP) on TCM manufacturing and we require a GAP inspection on the source of TCM before the GMP inspection for some TCM drug products.

Q You mentioned that the draft will be available on the Web site at the end of this year. Will there be a transition period for the local manufacturers and individuals overseas to make comments?

From left to right: Cheryl Siow, Paul N. D'Eramo, Robert W. Tribe, Robert P. Best, JiangYing Yan, WenZuo Chang, QingWu Guo, Prof. Zhongzhi Qian, Ai Liu, and Lili Cao.

QingWu Guo Definitely. The period will be at least three months or more to solicit opinions and suggestions twice.

Q How is the SFDA cooperating with ICH?

JianHua Ding ICH played a very important role in China's regulatory system. We adopted many guidelines from ICH in drafting our local technical guidelines. I believe ICH is not only very important for our regulatory system, but also for the industry. We send Chinese delegates to attend many ICH conferences to learn and study their progress. We also learn ICH guidelines through many ways. We organize several workshops each year with relevant ICH authorities, such as the ICH Global Cooperation Group (GCG). This helps us to study and understand ICH technical guidelines. In addition, we have several experts who have been involved in the drafting of ICH guidelines, such as ICH Q10 and Gene Therapy guidelines.

I am involved in ICH Q10. The SFDA also sends people on behalf of the Life Science Innovation Forum (LSIF) to the ICH GCG. In February, ICH GCG invited six country members, including China, to attend the ICH GCG meeting in Portland.

Q Will the SFDA plan to apply for PIC/S?

QingWu Guo We know that PIC/S is recognized as an excellent GMP inspection cooperation organization. There is mutual learning, information, and resource sharing among the members. We feel that there is mutual recognition in PIC/S. Therefore, we think we could benefit a lot by mutual sharing in PIC/S.

As PIC/S is a country membership, we believe participation of China in PIC/S will promote GMP development.

Continued on page 40.

UNLOCKING VALIDATION SOLUTIONS

As a multinational contract validation service provider,
Validation Technologies Inc. is committed to providing the highest quality validation services and personalized support.

- Quality and Regulatory Services
- Project Management
- Validation Master Plans
- Computer Validation
- Cleaning Validation
- Process Validation
- Commissioning & Technical Services
- Clean Room Certification
- Third Party Certification Process
- Temperature Mapping
- Qualification of Pharmaceutical, Neutriceutical, Medical Device, and Biotechnology Facilities to meet EU, FDA, and any other International Regulations

Validation Technologies, Inc. is pleased to announce the establishment of a new representative office in Shenzhen, China. This presence in the global market further advances VTI as a leading validation service and cGMP consulting firm in the biotechnology industry.

Additional offices in San Diego, Los Angeles, San Francisco, Scottsdale, Boston, Philadelphia, Toronto, and Puerto Rico. We look forward to welcoming you to our new office in China!

Validation Technologies, Inc.
11590 W. Bernardo Court, Suite 245
San Diego, CA 92127
Phone (800) 930-9222
Fax (858) 673-3677
validation@validation.org

Validation Technologies, Inc. (Shenzhen)
19 Gaoxinzhongyi Road, Nanshan District,
Shenzhen, P.R. China
Phone: 86-755-86142174
vti.china@validation.org

For more information visit
www.validation.org

"...China has 4,682 companies which are API and drug manufacturers. Among them, 1,900 companies are TCMs manufacturers. A lot of companies produce Chinese medicines, chemical drug, and biological products at the same time."

However, being a nation with a 1.3 billion population and more than 4,600 manufacturers, we are evaluating the participation in PIC/S. You will hear our voice on this in the near future.

WenZuo Chang I would like to introduce you briefly to the international cooperation mechanism and general situation of the SFDA.

The SFDA attaches great importance to and participates diligently in the international exchange and cooperation on drug administration including international activities of drug safety. We actively develop collaborations with international organizations and other national drug regulatory agencies around the world.

In regard to the cooperation with government agencies, we have signed a cooperation agreement or Memorandum of Understanding (MOU) with more than 10 agencies from the US, Canada, France, the UK, EMEA, Italy, Australia, Cuba, Brazil, South Korea, Singapore, Thailand, etc. Therefore, SFDA has preliminarily formed the pattern of intensive cooperation combined with extensive cooperation with its foreign counterparts.

Very importantly in the international cooperation, the SFDA pays close attention to reinforcement of the cooperation on traditional medicines, for China, they are TCMs and ethnic medicines. The SFDA has good cooperation on TCMs and herbal medicines standards with the WHO, Forum of Herbal Medicine Harmonization (FHH), in the Western Asia Pacific Region and a number of countries, such as the US, France, the UK, the Republic of Korea, etc.

In addition, we also have cooperation with governmental international organizations and other international organizations in the drug regulatory sector, especially with the WHO in facilitating the system of national essential medicines, GMP, traditional medicines, the enhancement of vaccine management, and the development of anti-malaria medicines, which has achieved positive results. The cooperation is on the basis of mutual benefits. In the international activities, we also perform the international obligations meticulously, and always refer to the international best practices and experiences in drug administration and practice it under the Chinese context, for instance, in those mentioned by Mr. Ding and Mr. Guo regarding the cooperation with ICH, and considering to participate in activities of PIC/S. The SFDA has learned lots of valuable experiences, shared from the all international activities, which helps in raising the level and capacity of China's drug administration and to be in line with the international practice.

Q Will the SFDA set up a special inspection department for TCM?

QingWu Guo I would like to clarify that China has 4,682 companies which are API and drug manufacturers. Among them, 1,900 companies are TCMs manufacturers. About 40% of the drug manufacturers are TCMs manufacturers. A lot of companies produce Chinese medicines, chemical drug, and biological products at the same time. There are more than 800 manufacturers which produce TCM preparations only. SFDA has a Division responsible for registering TCMs in the Drug Registration Department. Other than this, we do not have other specific departments for regulating TCM; however, we do have specialists responsible for that.

JiangYing Yan Let me add that during the development of Chinese medicine in our country, we need to ensure safety and quality while we reserve the tradition and encourage innovation at the same time. As what has been applied to chemical drugs, the first priority is to ensure the safety and effectiveness.

Q How can ISPE be supportive of the Chinese pharmaceutical industry?

QingWu Guo Based on my understanding of ISPE, your organization has a lot of cooperation with the China Center for Pharmaceuticals International Exchange (CCPIE). I suggest ISPE look into two areas should you wish to have a wider cooperation with China. First is to establish cooperation with the China pharmaceutical industry, such as through exhibitions and forums/conferences, as what ISPE has done during China-Pharm this year. My second suggestion is to cooperate with government agencies, e.g., the SFDA by providing GMP training to inspectors or assistance with on-the-job training in international inspections. For example, we have trained 100 inspectors on international inspections. Perhaps ISPE could support us in this area. Another aspect of cooperation will be providing comments and suggestions after we announce the GMP revision.

We also hope ISPE can recommend to us the latest information on the GMPs. We understand that ISPE has many of the latest guidances, requirements, and standards. We know that ISPE has a great pool of technical experts worldwide on developing practical standards, which I believe will be very useful to help improve the GMP activities in China.

Zhongzhi Qian I would like to introduce the international cooperation development on drug standards. Drug standards have been widely communicated between countries and many cooperation relationships have been established with many countries. We

have developed international cooperation through three channels: First, the WHO, second, the National Drug Regulatory Agency, and third, the international organizations on drug standards.

I would like to focus on the international cooperation situation on TCM standards. We started cooperation with the WHO in 1979 when Mr. Yuan Shicheng, the Secretary-General of the Chinese Pharmacopoeia Commission was nominated as WHO Foreign Expert for the first time. In 2002, China, Japan, Korea, Singapore, Vietnam, Australia, and Hong Kong SAR established the Western Asia Pacific Forum of Herbal Medicine Harmonization (FHH) under WHO's initiative. FHH's goal is to promote the coordination and development of traditional and herbal medicines standards within Western Asia Pacific countries.

On the subject of cooperation with the National Drug Regulatory Agency, there is effective cooperation between the SFDA and the French AFSSAPS. We have had cooperation since 2000. We have 27 Chinese crude drugs recorded in the French list of medicinal plants, of which seven are in the French pharmacopoeia, and five were recommended into the European pharmacopoeia by the French pharmacopeia.

With regard to cooperation with international organizations on drug standards, we have had cooperation on cooperative research and mutual recognition mechanism of TCM standards with the US, European, and British pharmacopoeias. In April 2008, an MOU was signed with the USP for 2008-2010, which is an extension of the MOU for 2005-2007. The MOU covers the drug standards between the two countries. First is the harmonization of the analytical methods, and then the cooperation and coordination on drug standards focusing on TCMs, as well as on chemical and biological products.

JiangYing Yan ISPE has a strong body of technical knowledge and resources, including standards, regulations, technical documents; these will really help our pharmaceutical industry and drug supervision. In the future, we at SFDA, including CCPIE, will further strengthen cooperation with ISPE.

This report presents the results of the FMI/CMAA Ninth Annual Survey of Owners and provides insight into how companies with ongoing capital construction programs manage risks on projects.

Beyond the Bell Curve: A Report on Managing Capital Project Risk

by Jeff Lukowski and Mark Bridgers

Complexity creates risk and drives an increase in both its frequency and impact. In a world that is growing more complex, global, and interconnected in ways poorly understood, but recently revealed during the US financial crisis, a better way to manage construction risk is a necessity. The results of the Ninth Annual Survey of Owners, recently conducted by the Construction Management Association of America (CMAA) and FMI Corporation, will focus on providing a better way to manage construction risk.

Owners, contractors, engineers/architects, and material or equipment suppliers are just a few of the players that are involved and participate in the construction of facilities and infrastructure. While this study is targeted at understanding owners' perspectives, the risk mitigation strategies they choose to employ, and their ramifications are applicable to all players. In this study, these risk mitigation strategies are divided into four categories: Accept and Manage, Accept and Transfer, Recognize and Ignore, and Avoid. Within each category there are numerous potential strategies. The top five strategies for managing risks are: 1. Integrate Risk into the Contract, 2. Use Standardization, 3. Hire Internal Staff, 4. Increase Team Meeting Frequency, and 5. Request Budget Increases.

Four risks exhibited both very high frequency and major impacts to capital construction projects. Governmental regulation, inaccurate budgeting or estimating by the owner, availability of qualified construction firms and worldwide commodity demand. The first is forced upon many owners and requires strategies focused on influencing the development and application of these regulations. The second is self-created in many instances, due to a lack of recognition of the improbable event, what Nassim Nicholas Taleb describes as a Black Swan in his recent book, "The Black Swan." The latter two revolve around market supply and demand issues. The frequency of all four of these risks dictates that they are routinely managed by owners and when possible transferred.[1]

The reader is encouraged to keep the following in mind as he/she considers how to mitigate risk in today's capital construction world.

- Using past history as a guide for understanding future risk is necessary, but not all encompassing – history is less applicable today because complexity is changing the nature of the game.
- The design and construction mind searches for historical order and patterns to better understand the environment; yet random events will happen. The most severe impacts to capital construction programs noted by the survey respondents fall into the Cost Other = Unanticipated Costs category where they related unpredicted, one-time events that devastated the project or program.
- It is much easier to plan, obtain financing, and hire service providers by ignoring the possibility that a Black Swan-type event may take place, but take place it will.
- History takes the sharp edges off unpredicted, one-time events that devastated the project, compelling practitioners to underestimate the probability that a one-time event is not really a one-time event. The destruction of the Wheeling Suspension Bridge in 1849 and subsequent destruction of the Tacoma Narrows Bridge in 1940 is an example.
- Focusing on the well-defined sources of uncertainty is the normal practice in the industry where numerous experts prepare writing and research to identify an all-encom-

Continued on page 44.

ELETTRACQUA

pure water technologies

SINCE 1966

PHARMACEUTICAL WATER SYSTEMS

DOUBLE PASS REVERSE OSMOSIS HIGH TEMPERATURE SANITIZATION

DESIGN AND CONSTRUCTION OF PURIFIED WATER PACKAGES • DOUBLE PASS REVERSE OSMOSIS • R.O. + ELECTRODEIONIZATION HOT WATER SANITIZABLE • ULTRAFILTRATION • MULTIPLE - EFFECT DISTILLATION UNITS • PURE STEAM GENERATORS • STORAGE AND DISTRIBUTION LOOP • COMPLETE TURN KEY PROJECTS • VALIDATIONS IQ, OQ

www.elettracqua.com

visit us at
ACHEMA 2009
Frankfurt am Main/Germany
11.–15. 5. 2009
hall 4.1 - stand L20/L22

Highest Frequency Risks	Software Highest Impacting Risks*	Favorite Strategies, Tactics and Processes
1. Commodity Demand	1. Estimating Accuracy	1. Integrate Risk into the Contract
2. Energy Prices	2. Government Regulations	2. Use Standardization
3. Skilled Craftsmen	3. Commodity Demand	3. Hire Internal Staff
4. Estimating Accuracy	4. Construction Firms	4. Increase Team Meeting Frequency
5. Construction Service Demand	5. Construction Service Demand	5. Request Budget Increase
* excluding self-selected other responses		

Table A. Top five risks and strategies.

passing list of design and construction risks – we must see the forest *and* trees for success, recognizing that the most devastating risks will originate from the forest, which is harder to see and discuss.

Survey Highlights

The highest-observed frequency and impact risks, along with the favorite strategies, tactics and processes to address them, are detailed in Table A. The highlights of the survey include the following:

- **Throwing Money at the Problem:** 33 percent of the time owners request a budget increase to manage project or program risks.
- **Application of Leverage:** 75 percent of the time owners use some form of program-level purchasing power to transfer or manage project or program risks.
- **Hammer Looking for a Nail:** 25 percent of the time owners use the same strategy, tactic, or process to address both frequency and impact (severity) without recognizing the different challenges of each.
- **Tunneling:** Seven out of 28 survey risks were rated with both low frequency and impact, indicating a focus on a few well-defined sources of risk.
- **Black Swans Do Exist:** With only two exceptions, an "immense" impact was reported by multiple survey respondents in every risk description presented, indicating that every risk has the potential for catastrophe.
- **The Impact of the Highly Improbable:** "Major" and "Immense" impact were most frequently reported in "Cost Other = Unanticipated Risks" category where respondents described unpredicted, one-time events that devastated a project or program 22 percent of the time.
- **Greatest Fear:** Schedule impact was described as the greatest negative outcome to project or programs; nearly twice as many "Major" and "Immense" impacts were described versus the other impact categories of financial (cost) or qualitative (public or internal reputation, quality or safety).
- **Size Matters:** The biggest capital construction programs choose to "Accept and Manage" risk nearly 70 percent of the time (50 percent more than the smallest programs that "Avoid" or "Accept and Transfer" nearly 60 percent of the time).
- **Risk Appetite Matters:** Financial institutions, real-estate developers, and sports authorities have the lowest risk appetite and frequently choose to "Avoid" or "Accept and Transfer" risk, while chemical companies, energy firms, and various types of manufacturers tend to have the highest risk appetite and "Accept and Manage" risks frequently.
- **Consistent Strategy Use:** Owners elect to either "Accept and Manage" or "Accept and Transfer" the 28 risks included in the survey 61 percent and 22 percent of the time, respectively.
- **Avoidance:** 41 percent of the time when inability to effectively plan is perceived as a risk, owners prefer to avoid the project rather than ignore, manage, or transfer the risk.
- **Management:** 38 percent of the time when inability to estimate accurately is perceived as a risk, owners prefer to accept and manage the risk rather than avoid, ignore, or transfer.

Risk Management Focus

The focus of the FMI/CMAA *Ninth Annual Survey of Owners* is on understanding how program- or project-level risks are assessed and managed prior to or during project execution (planning through turnover) and how they impact an owner's overall capital program. Life Science industry participants represented more than ten percent of the total participation. FMI analyzed the frequency of occurrence and severity of impact of specific risks, and more broadly, how owners tend to manage construction risks by electing to use certain strategies, tactics or processes.

FMI/CMAA worked with a team of highly experienced industry professionals to establish a common definition of risk management in the survey. Although the general topic of risk management in the construction industry covers a broad range in scope (e.g., insurance, bonding, litigation, operations, economic, etc.), we settled on the following definition:

> *"Risk management for projects in the construction industry consists of a process where risks are identified and quantified, and opportunities for mitigation are discovered. Owners involved in construction will make decisions about how to mitigate risks, which may include elements of accepting, reducing, sharing, transferring, or avoiding the risk. Ultimately, risk management involves the implementation of the mitigation plan."*

FMI/CMAA designed the survey in order to develop a basic understanding of how owners today, including those in Life Sciences, are managing risk in construction projects. In order to accomplish this, we set out to understand owner behavior when faced with a given set of risks. FMI and CMAA believe owners make risk mitigation decisions in their capital construction programs according to the degree of assumed own-

Figure 1. Risk mitigation decision matrix.

ership and the selection of a passive or active risk management approach. These decisions fall within a two-by-two matrix as proposed in Figure 1.

"Recognize and Ignore" and "Accept and Manage" are categories where the risk management strategies, tactics, or processes employed result in a high degree of ownership exhibited by the owner. Risks that owners perceive as difficult to influence, including security requirements or energy prices, are typically recognized and ignored. In extreme cases, this risk can destroy a project. Risks that are believed to be subject to influence are typically accepted and managed. These include construction management talent or estimating accuracy.

"Avoid" and "Accept and Transfer" are categories where the risk management strategies, tactics, or processes employed result in a low degree of ownership exhibited by the owner. Risks that owners perceive as severe and uncontrollable are the most actively analyzed and likely to be avoided.

"Accept and Transfer" and "Recognize and Ignore" are categories where the risk management strategies, tactics, or processes employed are more passive. In the first case, the owner pushes responsibility to actively manage the risk onto a third party. In the second case, ignoring the risk requires no action.

"Accept and Manage" and "Avoid" are categories where the risk management strategies, tactics, or processes employed are more active. In the first case, the owner actively takes on responsibility to manage the risk for his/her own account with his/her own staff. In the second case, an active investigation of the risk indicates that it is severe and uncontrollable and dictates the owner must take action to remove the exposure to the risk.

"Accept and Transfer" and "Accept and Manage" are opposites of one another in the owner's perspective in that the first pushes risk to an external party for active management, while

Continued on page 46.

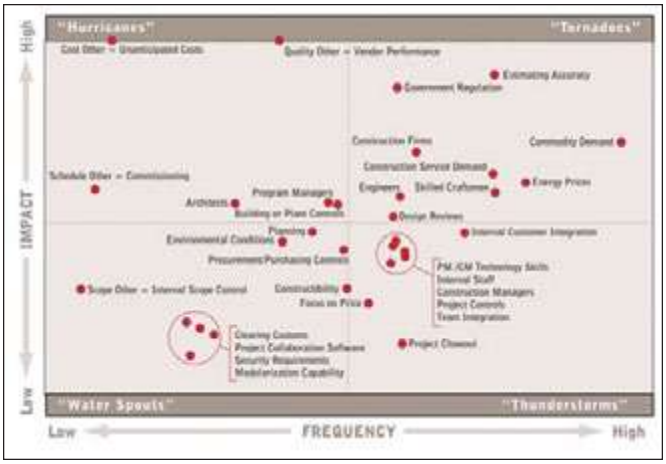


Figure 2. Frequency vs. impact aggregate scores.

the second retains the risk internally for active management.

"Avoid" and "Recognize and Ignore" are opposites of one another in the owner's perspective in that the first requires action to remove the exposure to the risk, while the second requires no action.

While owners prepare lists of known risks that may occur, research suggests that owners are reluctant to consider pessimistic scenarios while performing risk assessments.[2] These pessimistic scenarios are outside of this matrix in that they are not considered. Nassim Nicholas Taleb refers to these pessimistic scenarios as little Black Swans and he describes a set of more severe outcomes as the Unknown Unknowns or true Black Swans.

A Construction Black Swan

The Tacoma Narrows Bridge was one of the most spectacular failures in engineering history. This suspension bridge used a stiffened-girder design rather than the customary and necessarily deeper open truss. This innovative design gave a slender silhouette whose appearance was dramatic and graceful, albeit inappropriate for the site conditions. The last spectacular undulating motions of the roadway being twisted to destruction were recorded on newsreel film even as engineers were trying to understand the phenomenon of its aerodynamic instability.

Othmar Ammann, designer of the George Washington and other monumental bridges wrote:

> *"...the Tacoma Narrows bridge failure has given us invaluable information…It has shown [that] every new structure which projects into new fields of magnitude involves new problems for the solution of which neither theory nor practical experience furnish an adequate guide. It is then that we must rely largely on judgment and if, as a result, errors or failures occur, we must accept them as a price for human progress.*[3]"

The possibility of failure of the Tacoma Narrows Bridge because of a steady crosswind of 42 miles per hour was unforeseen by its designers. Nassim Nicholas Taleb refers to this as tunneling[4] or "we focus on a few well-defined sources of uncertainty... at the expense of the others that do not easily come to mind."

If the designers of the Tacoma Narrows had known the story of the Wheeling Suspension Bridge, the longest span in the world when it was completed in 1849, they would have anticipated that wind could be a possible cause of failure. The Wheeling bridge was destroyed in a storm. In this older incident, the technical literature on the design and ultimate failure of this bridge was not well-documented even though a local reporter made detailed observations of the bridge as it experienced similar undulation, due to relatively modest crosswinds.

Survey Results

Risks

A meaningful discussion about program and project-level risks is undertaken in the context of the perceived frequency and impact of that risk. There are hundreds, if not thousands, of possible risks that an owner may face when managing a construction project or program. A considerable effort was made to narrow the list of risks based on the idea that owners tend to focus on what they have previously experienced as opposed to what they have not experienced. Said a different way, owners manage the risks they know as opposed to what they do not know. FMI selected 28 specific risks and an additional four respondent-chosen risks which were tied to four areas of impact to the owner: 1. Quality, 2. Cost, 3. Schedule, and 4. Scope.

Respondents were asked to define any other risks that impact them in the areas of quality, cost, schedule, and scope. FMI selected a name for these risks based on frequency of mentions: Quality Other = Vendor Performance, Cost Other = Unanticipated Costs, Schedule Other = Commissioning or Turnover, and Scope Other = Internal Scope Control.

In Figure 2, FMI plotted each of the original 28 risks along with the four self-described risks into quadrants describing their perceived frequency and impact. High-frequency and high-impact risks are referred to as "Tornadoes." Nine risks fall into this quadrant with governmental regulation, inaccurate budgeting or estimating by the owner, and commodity demand exhibiting the combined highest frequency and severity. Risks in which the perceived frequency was high and impact was low are referred to as "Thunderstorms." Nine risks fall into this quadrant with internal customer integration representing the greatest frequency and one of the highest impacts in this quadrant.

Risks in which the perceived frequency was low and impact was low are referred to as "Water Spouts." Eight risks fall into this quadrant with a group of four, including Clearing Customs, Project Collaboration Software, Security Requirements, and Modularization Capability, perceived as exhibiting little impact. There can be two explanations for the perception of both low impact and frequency: 1. These risks actually result in an insignificant impact or 2. The assessment of impact is incomplete. As described previously, the fact that a particular risk is perceived as having low impact

is not the same as saying it cannot have high impact – we must see the forest *and* trees for success, recognizing that the most devastating risks will originate from the forest which is harder to see and discuss. Risks in which the perceived frequency was low and impact was high are referred to as "Hurricanes." Six risks fall into this quadrant with two exhibiting major or immense impacts, Cost Other = Unanticipated Costs and Quality Other = Vendor Performance. In Figure 2, these two risks are not depicted to scale and exhibited an impact twice as high as estimating accuracy.

Highest-Impact Risks

FMI studied how each risk impacted overall project success through the three basic attributes of the job: cost (financial), time (schedule), and qualitative (e.g., quality, reputation, and safety) areas. Participants were asked to score each attribute as either not applicable, no impact, minimal impact, moderate impact, major impact, or immense impact.

Each risk was ranked from the highest to lowest total impact for each attribute, and this is shown in Figure 3. For each risk, the bar length represents perceived severity (e.g., estimating accuracy is perceived to have a major reputational impact, moderate quality impact, and minimal safety impact). For example, the risk of Cost Other = Unanticipated Costs ranks the highest in both Financial and Schedule impacts, whereas Quality Other = Vendor Performance ranks the highest in Schedule impacts. Impacts to the schedule

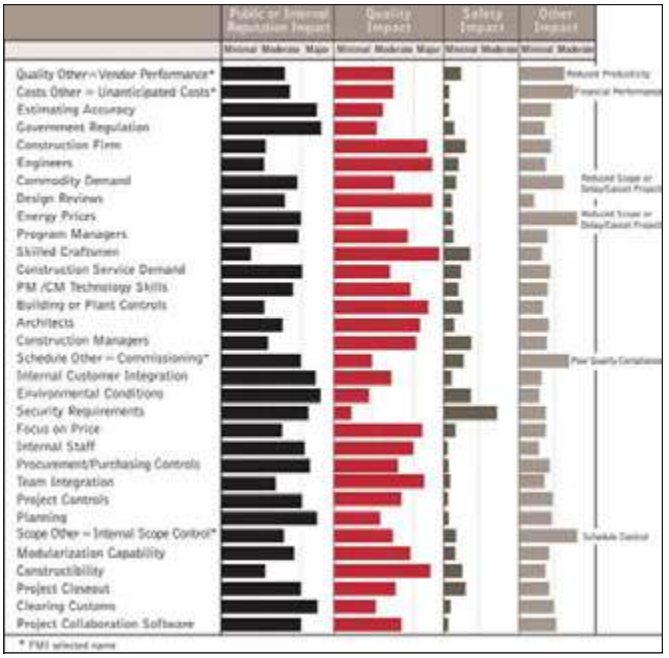


Figure 3. Qualitative impacts for each risk.

were twice as high (bad) on average as the financial impacts and the qualitative impacts. Therefore, schedule impacts proportionately influenced the total overall impact rank.

Schedule impacts are damaging because in some cases,

Continued on page 48.

Risk Category	Financial Impact Rank	Schedule Impact Rank	Qualitative Impact Rank	Total Impact Rank
Quality Other = Vendor Performance	2	2	1	1
Cost Other = Unanticipated Costs	1	1	2	2
Estimating Accuracy	3	4	3	3
Government Regulations	14	3	4	4
Commodity Demand	4	6	7	5
Construction Firm	8	8	5	6
Construction Service Demand	13	7	12	7
Energy Prices	5	10	9	8
Schedule Other = Commissioning	21	5	17	9
Skilled Craftsmen	7	14	11	10
Engineers	12	15	6	11
Program Managers	17	12	10	12
Architects	6	9	15	13
Building or Plant Controls	9	11	14	14
Design Reviews	10	19	8	15
Planning	25	13	26	16
Internal Customer Integration	22	17	18	17
Construction Managers	11	22	16	18
Environmental Conditions	24	16	19	19
Project Controls	15	20	25	20
Focus on Price	19	21	21	21
Internal Staff	18	18	22	22
PM/CM Technology Skills	20	25	13	23
Team Integration	16	23	24	24
Scope Other = Internal Scope Control	26	24	27	25
Procurement/Purchasing Controls	27	26	23	26
Constructibility	23	27	29	27
Modularization Capability	28	29	28	28
Security Requirements	29	31	20	29
Project Collaboration Software	30	28	32	30
Project Closeout	31	30	30	31
Clearing Customs	32	32	31	32

Table B. Impact ratings for each risk.

there is little that can be done by a project manager to rescue a project once a major schedule delay occurs. These delays cannot be easily resolved with a scalar approach, such as requesting a budget increase.

Participants were further asked to identify the specific qualitative impact type as either Public or Internal Reputation, Quality, Safety, or Other as a self-selected impact. This is shown in Table B. The risk with the largest public or internal reputation impact is government regulation. The risk with the largest quality impact is an inability to find or attract sufficient and trained skilled craftsmen, and the risk with the largest safety impact is, not surprisingly, security requirements.

An example of public perception impacts is the scenario of constructing highly pressurized lines snaking under farms and past residential areas. This will raise fears about safety and environmental impacts in communities along these pipeline routes. Companies building pipelines face lawsuits, eminent-domain battles, and jurisdictional fights among the local, state, and federal authorities that oversee the projects. Two New England projects have been held up or canceled in recent months because of local opposition.[5]

Skilled craftsmen carries the highest quality impact potential. Kenneth D. Simonson, chief economist for the Associated General Contractors of America, said, "To the extent that people are picking college, they're turning down construction.[6]"

Risks rated with a combination of low frequency and impact may represent potential for Black Swan-type events. Figure 4 displays a select list of low-frequency and low-impact risks (Water Spouts) from Figure 2 and breaks down the frequency of observation for each type of owner. Public and private entities make up nearly 75 percent of the frequency rating of clearing customs risks. Put another way, government agencies do not observe clearing customs issues, which suggests that their projects source materials and equipment domestically.

Modularization capability (capital construction program at risk due to inexperienced modularization installation contractor) scored 38 percent of the impact by respondents (firms) with the average project size of $15 million to $50 million. Meanwhile, projects between $100 million and $500 million expect to see 40 percent of the impacts related to project collaboration software (capital construction program at risk due to ineffective use of project collaboration software) than any other risk. Many owners reported that they also would like to convince their Procurement and Legal departments of the benefits of a collaborative delivery method to improve risk management.

Engineering News Record[7] reports that many are fearful of the transition to Building Information Management (BIM), outlining a long list of possible and increased exposure. FMI's *Eighth Annual Survey of Owners*;[8] however, concluded that

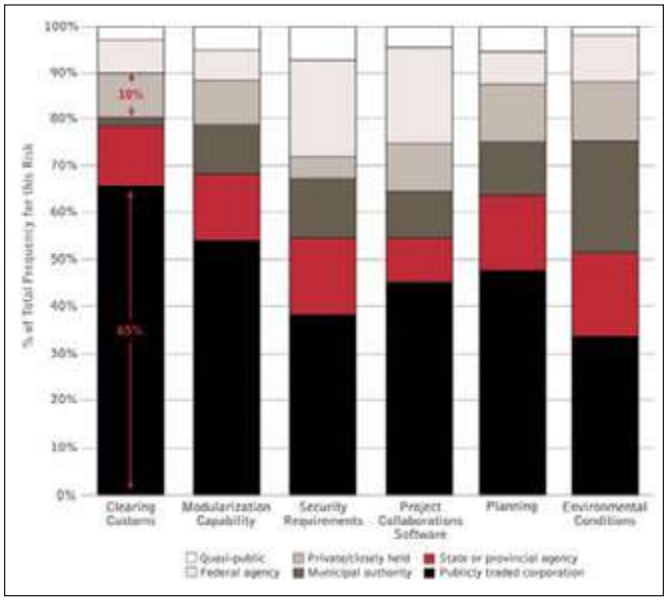


Figure 4. Percent of risk observation frequency by organization type.

Continued on page 50.

ARE YOU RELYING ON SAFETY PRODUCTS THAT *"SHOULD"* WORK?

FIKE IS COMMITTED TO RELIABLE SAFETY SOLUTIONS THROUGH RESEARCH, NEW TECHNOLOGIES, AND EXTENSIVE TESTING.

EXPLOSION PROTECTION • PRESSURE RELIEF • TESTING SERVICES

- Comprehensive selection of ASME, CE and 3-A rupture/bursting discs
- High performance explosion vents, specifically designed for sanitary applications
- Complete line of products designed for CIP/SIP applications
- Dedicated Team of Combustion Engineers and Pressure Relief Experts

DON'T LEAVE THE SAFETY OF YOUR BUSINESS TO ANYTHING LESS THAN THE MOST RELIABLE, PROVEN PRODUCTS.

EXPLOSION VENTING

EXPLOSION SUPPRESSION

RUPTURE DISCS

FULL-SCALE TESTING

Fike®

WWW.FIKE.COM

PROVEN PERFORMANCE, QUALITY AND RELIABILITY FOR OVER 60 YEARS

1-866-758-6004

"…we have to manage the risk that our knowledge will find its way into our competitors' hands through the use of foreign-based consultants, engineers, and contractors."

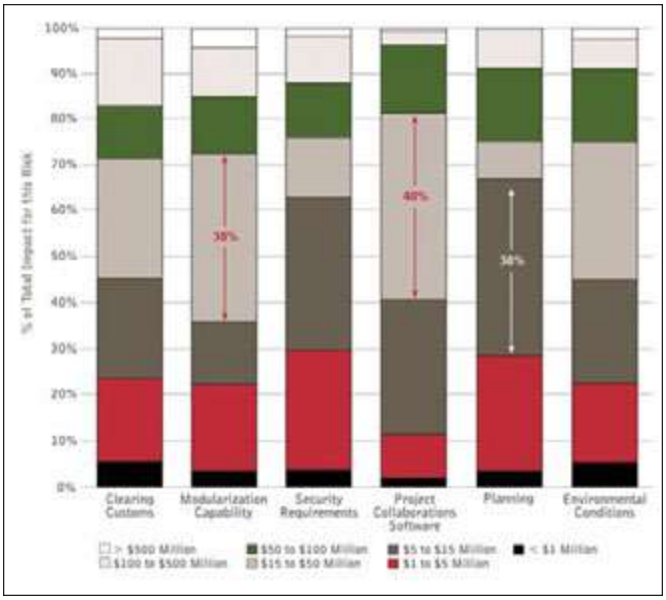


Figure 5. Percent of impact of select risks by average project size.

approximately "35 percent of all respondents have used BIM processes and technology to reduce the frequency and severity of loss." Interestingly, projects between $5 million and $15 million perceive 38 percent of the impacts as a result of planning (capital construction program at risk due to no or ineffective use of pre-project, resource, and short-interval planning techniques) than any other respondent's average project size. Projects in this range may experience major or immense cost and schedule impact if the scope changes dramatically. This is described further in Figure 5.

One participant at a large chemical company was quoted describing a risk that often goes overlooked in today's design and construction environment: "Import/export refers to protecting intellectual property and technology. This wasn't an issue 20 years ago, but we have to manage the risk that our knowledge will find its way into our competitors' hands through the use of foreign-based consultants, engineers, and contractors."

Strategies, Tactics, and Processes

The strategies, tactics, and processes are included in the mitigation plan for each risk, along with ownership assignment, costs, and timing. Unique strategies for mitigating capital project risk likely number in the hundreds. When respondents were asked which strategies they use most often, they integrate risk into contracts 74 percent of the time, while requiring an equity involvement only 10 percent of the time. This trend should continue as traditional financing is harder to obtain and Public Private Partnerships (P3) become more acceptable. Figure 6 demonstrates that owners continue to transfer risks to service providers through contractual mechanisms and language more frequently than any other approach. Using a standardized process or approach was the second most popular method at 71 percent of the time. Owners could select and apply more than one strategy at a time.

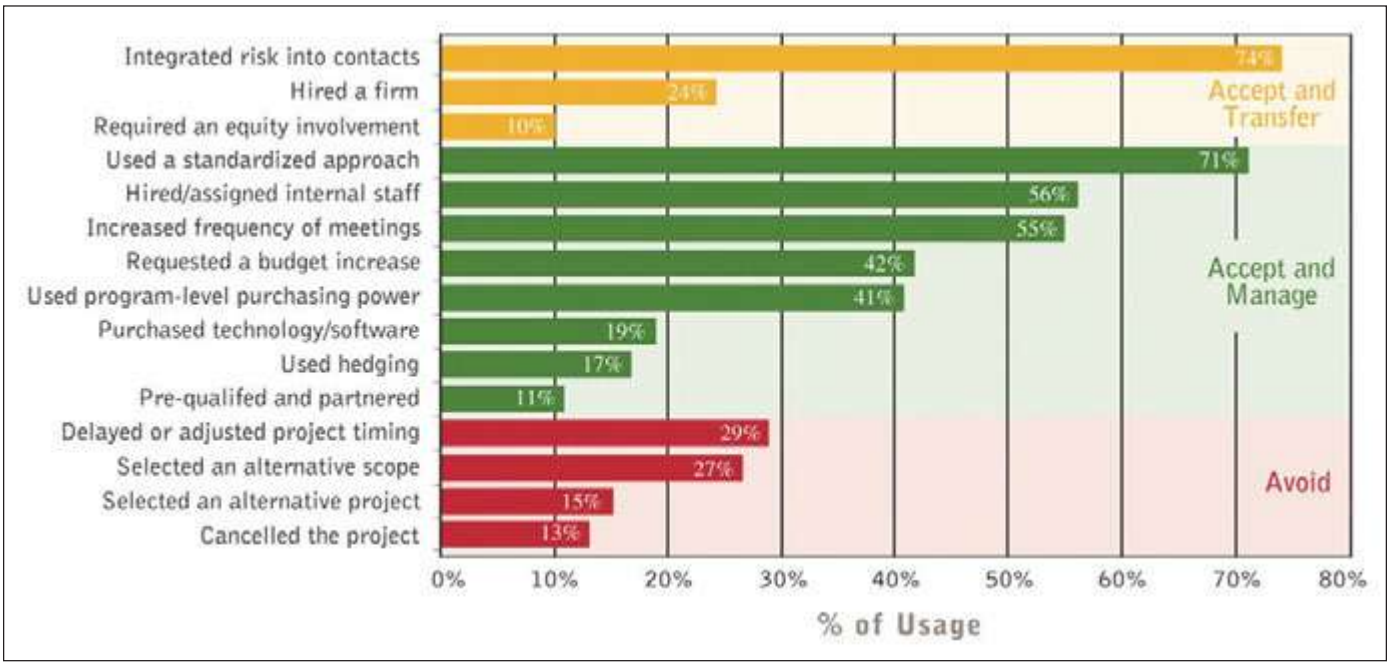


Figure 6. Ratio of usage of strategies, tactics and processes.

Continued on page 52.

DeltaV Batch.

The perfect cup. Every time.

Easy.

Emerson understands your need to quickly respond to varying customer requirements. That's why we designed DeltaV Batch to give you the robust, repeatable performance that lets you assure your customers of a perfect, on-spec batch. First time. Every time. Easy.

From seamless integration with your enterprise planning and manufacturing execution systems to modular, class-based configuration and integrated change management, DeltaV Batch simplifies your batch operations.

Enabling agile manufacturing has never been easier. So, grab yourself a fresh cup and visit: **EasyDeltaV.com/Batch**

DeltaV™

EMERSON™
Process Management

EMERSON. CONSIDER IT SOLVED.™

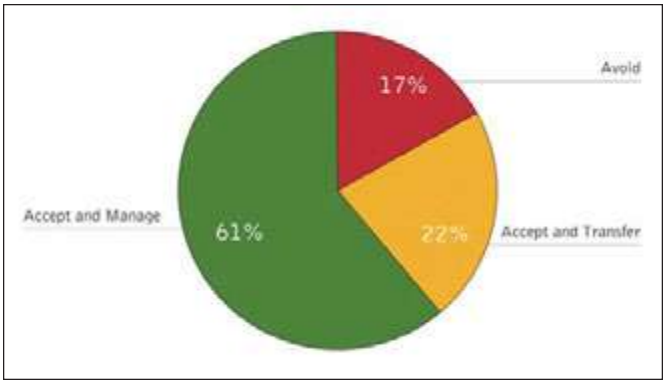


Figure 7. Choice of strategy.

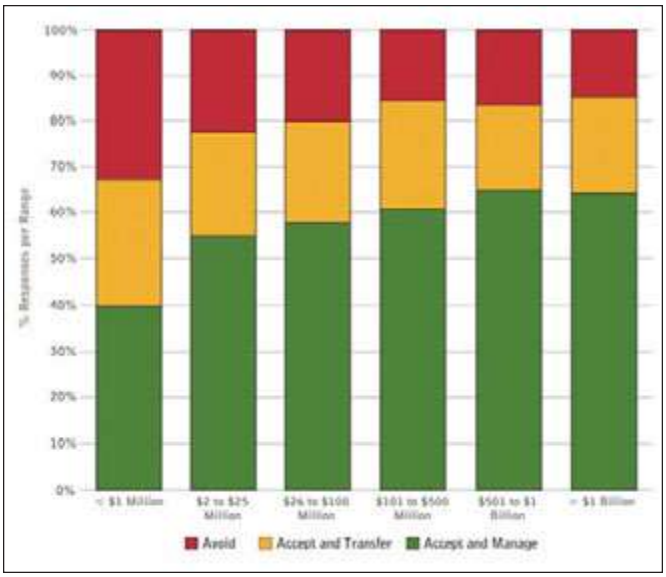


Figure 8. Strategies used by capital program size.

FMI/CMAA found that on average, 61 percent of the time owners are accepting and managing risks, 22 percent of the time owners are accepting and transferring risks, and the balance of time they avoid risks as shown in Figure 7.

Figure 8 indicates an increasing desire to manage risks internally by the owner as the size of the capital program increases. Owners with less than $1 million spending manage their own risks 40 percent of the time, whereas owners that exceed $1 billion spending tend to accept and manage risks 65 percent of the time. This trend also parallels declining appetite to avoid risks. Owners become less likely to avoid a risk as their budget for capital projects increases. This suggests that owners with large capital programs are seeking larger returns and are more willing (or blind) to subject themselves to the risks inherent in these types of projects.

Each survey participant was categorized by FMI into one construction type to analyze his/her approach to risk management by this construction type. The segregation ignores the fact that many owners complete construction of multiple types in the same project (e.g., a typical life sciences facility might have both laboratory and commercial building space). Figure 9 shows that financial, real estate, and government types of construction all take a more conservative approach to risks and avoid them as a preferred strategy. Real estate and sports-oriented projects tend to transfer risks more often than other types of strategies. These types of projects are frequently one-time interactions between owner, designer, and contractor, and pushing risk to another party has minimal long-term consequences for the owner. In the case of owners who have programmatic work year in and year out, the more aggressive movement of risk to other parties tends to have more severe consequences. Life Sciences participants tend to Accept and Manage risks to the same extent as other process-intensive industries, such as Chemical, Energy, and Manufacturing.

Strategies to Mitigate Risks

Participants in the survey were not directly asked how they addressed each risk. The results in this section are derived from statistical correlations of the risk frequencies, risk impacts, and use of particular risk mitigation strategies. We studied how owners react to risks based only on 1. The frequency of occurrence and 2. The potential impact that the risk would have upon their program. Participants also were not asked about any particular strategies related to ignoring risks because it is assumed that if an owner ignores a risk, no strategy, tactic, or process is used to mitigate it; thus, measurement would not be feasible. The results were inferred by low correlation coefficients associated with the other three classifications. Refer to Figure 10 and Figure 11 for this analysis.

The top strategies, tactics, or processes that were most consistently applied to address a particular risk are shown in

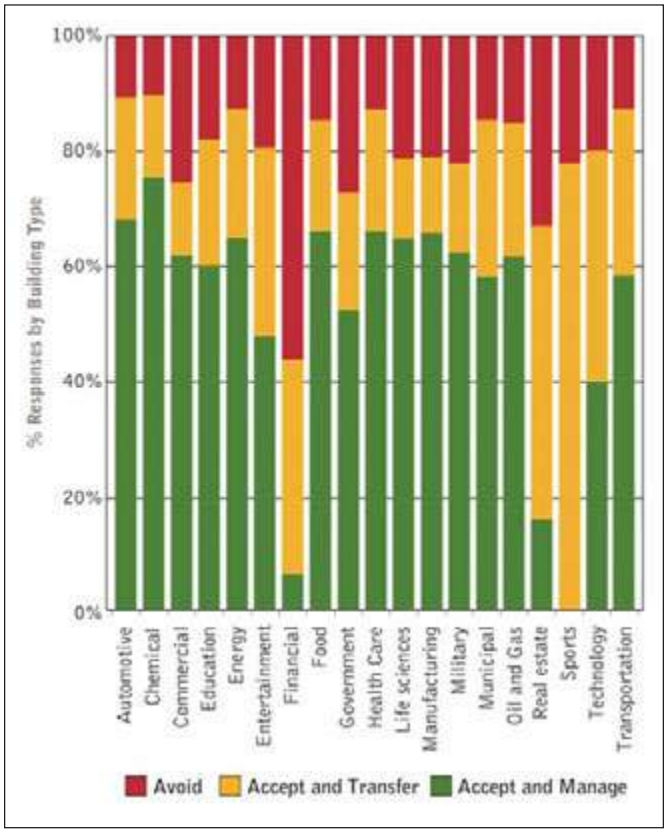


Figure 9. Strategic action by building type.

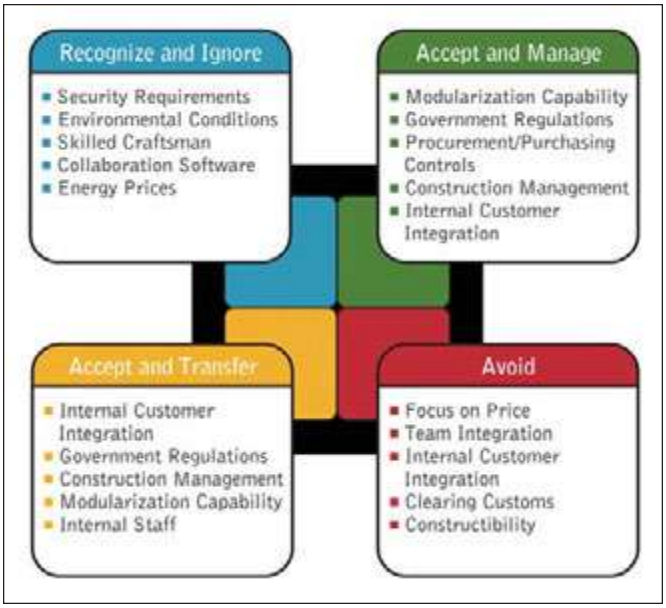


Figure 10. Connecting strategies and risks based on frequency of occurrence.

Table C. The risks that were originally scored as low frequency and low impact are italicized for emphasis. For example, owners that delay or adjust the timing of a project seem to do so when they are experiencing a risk due to an inability to attract qualified internal staff.

In 11 out of 32 risks evaluated in the survey, requesting a budget increase was the most employed strategy, tactic, or process – throwing money at the challenge. If project directors know that the tactic of getting more money is an accepted practice, they are going to be less concerned about cost-related impacts from risks. This explains the observation made in connection with Table B in which schedule impacts are of more concern to owners than financial and qualitative impacts.

Strategy, Tactic, or Process	Most Often Applied to Address These Risks
Selected an Alternative Scope	*Planning*
Requested a Budget Increase Team Integration Estimating Accuracy *Environmental Conditions* Project Closeout Government Regulations Focus on Price Constructibility Design Reviews Internal Customer Integration	Energy Prices
Cancelled the Project	Building or Plant Controls
Delayed or Adjusted Project Timing	Architects Internal Staff PM/CM Technology Skills *Clearing Customs*
Used Hedging	Construction Demand
Used Program-level Purchasing Power	Engineers Skilled Craftsmen Construction Firms Commodity Demand *Project Collaboration Software* Project Controls *Modularization Capability*
Purchased Technology/Software	Procurement/Purchasing Controls
Increased Frequency of Meetings	Program Managers Construction Managers *Security Requirements*

Table C. How specific risks are addressed.

Concluding Thoughts

Innovative owners, progressive corporate boards, and highly engaged capital construction teams are injecting risk management discussions routinely into their capital planning. FMI and CMAA believe this type of assertiveness is necessary across the industry and unfortunately too rare. The pace of change, design challenges, and financial complexity makes the process of capital construction higher risk and more challenging even for the most sophisticated owners. As reported earlier, 30 of 32 risks presented in this study were rated with multiple "Immense" impacts indicating catastrophic or Black Swan-type occurrences. Corporate boards now consider the "worst things" that could happen as a method of being engaged and monitoring the business risks.[10] CMAA and FMI are driving the industry toward this higher level of engagement. Use of a Certified Construction Management (CCM) professional, selection of aligned and efficient project delivery systems, and industry training in leadership and management are just three examples of how FMI/CMAA support this transformation.

Concludes on page 54.

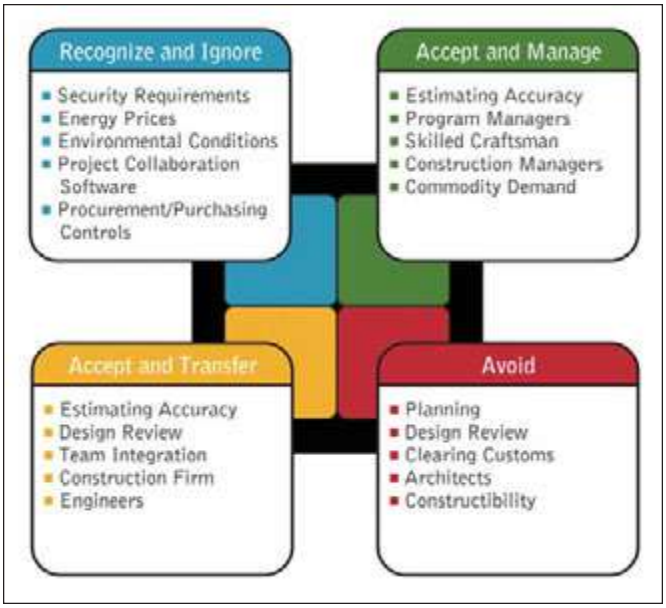


Figure 11. Connecting strategies and risks based on the potential impact.

More can be done and we believe successful owners will move "beyond the bell curve" in risk management of their projects. These efforts will recognize and take into account the following:

- History is less applicable today because complexity is changing the nature of the game.
- The most immense and severe impacts to capital construction programs are unpredicted, one-time events.
- Black Swan-type events will take place and recognizing their range of impact is more critical than attempting to predict when they might occur.
- Work to specifically avoid underestimating the impact and likelihood of improbable events and understanding the nature of more frequent risks.
- Focus on the "forest" as the source of the most devastating risks while managing the "trees" which are easier to see and discuss.

References

1. Nassim, Nicholas Taleb, Adapted from *The Black Swan (The Impact of the Highly Improbable)*, Random House, 2007, pg 50.
2. Touran, Ali, "Owners Risk Reduction Techniques Using a CM," Department of Civil and Environmental Engineering, Northeastern University, August 2006. CMAA-sponsored research.
3. Petroski, Henry, *To Engineer is Human, The Role of Failure in Successful Design*, Vintage Books, 1992, pp. 163-171.
4. Nassim Nicholas Taleb, The Black Swan (The Impact of the Highly Improbable), Random House, 2007, pg. 50.
5. Casselman, Ben, "Expansion of Pipeline Stirs Concerns Over Safety," Wall Street Journal, August 4, 2008.
6. Troianovski, Anton, "Skilled Trades Seek Workers," Wall Street Journal, August 19, 2008.
7. Speed, Vicki, "Strategies for Managing Risk in a New Era of Project Delivery," Engineering News Record, March 31, 2008.
8. FMI/CMAA *Seventh Annual Survey of Owners; C2 + 2C = LC, The Solution to Low Cost Capital Programs*, Fall 2006 publication, pp. 1-3.
9. FMI/CMAA *Sixth Annual Survey of Owners*, Fall 2005 publication, pg. 15.
10. Lublin, Joann S. and Tuna, Cari, "Anticipating Corporate Crises: Boards Intensify Efforts to Review Risks and Dodge Disasters," Wall Street Journal, September 22, 2008.

About the Authors

Jeff Lukowski has more than 15 years of experience in project planning and execution, manufacturing and process development in both the life sciences and chemical industries. He is a consultant with FMI Corporation specializing in streamlining capital construction programs for owners in the highly-engineered industries of chemical, life sciences, and utility/power generation. While improving performance of owner's construction organizations through standardization and process improvements, he also helps engineers, contractors, and vendors/suppliers identify new market opportunities. He has a BS in chemical engineering and a BS in environmental engineering from Michigan Technological University and a MBA from the University of North Carolina – Kenan Flagler Business School. He also is a Professional Engineer in the state of Michigan and a member of the ISPE Project Management Community of Practice. He can be contacted by telephone: +1-919-785-9213 or by email: jlukowski@fminet.com.

Mark Bridgers is a senior consultant with FMI and works with owners or purchasers of construction contracting services in the areas of organizational analysis, construction cost management, accounting and financial issues, and strategy development. He brings more than 15 years of construction industry expertise, including financial engineering, surety bonding, and reinsurance experience to FMI. He consistently implements cost-saving innovations and strategies for his owner clients, including building strong supplier relationships to manage the risks of low quality and diminishing craft labor. Bridgers holds a MBA from the University of Virginia's Darden School and a Bachelor's in financial management from Clemson University. He has earned the titles of Chartered Property and Casualty Underwriter (CPCU) and Associate in Reinsurance (ARe). He can be contacted by telephone: +1-919-785-9351 or by email: mbridgers@fminet.com.

FMI Corporation, 5171 Glenwood Ave, Suite 200, Raleigh, North Carolina 27612, USA.

2009

ISPE Training Events and Conferences Worldwide

Watch ISPE.org for details.

Tampa Conference: Implementing Development and Manufacturing Technology
2-5 March 2009, Tampa, Florida, USA

HVAC, *GAMP® 5* implementation, containment, aseptic and downstream processing, single-use technology, cleaning, biological contract manufacturing, and process validation in biotechnology

Brussels Conference on Enhanced Competitiveness – Sustainable Achievements
30 March-2 April 2009, Brussels, Belgium

HVAC: Good Practice and Innovations, *GAMP 5*, 21 CFR Part 11 and the EU GMP Annex 11, critical utilities, continuous process and process intensification, manufacturing excellence and R&D laboratories, containment, and calibration

Sponsorship and Exhibit Opportunities Available

Chicago Classroom Training
11-14 May 2009, Chicago, Illinois, USA

GAMP 5, water, HVAC, biotechnology, C&Q, Q7a, and technology transfer for finished dosage forms

Madrid Classroom Training
18-21 May 2009, Madrid, Spain

GAMP 5, water, technology transfer for API, HVAC, C&Q, and PAT

Washington Conference: Engineering Regulatory Compliance
1-4 June 2009, Washington, D.C., USA

PQLI, barrier isolation technology, critical utilities, integrated approaches to C&Q, validation, GMPs, global supply chain security, packaging challenges, GAMP Good Practice Guides on VPCS Ver. 2 and Calibration Management Ver. 2

Strasbourg Conference: Quality - Knowledge Through Science
28 September-1 October 2009, Strasbourg, France

Barrier isolation innovation updates and new case studies, investigational products, *GAMP 5* operational aspects, containment, disposables, PQLI, and C&Q

Philadelphia Classroom Training
5-8 October 2009, Philadelphia, Pennsylvania, USA

HVAC, *GAMP 5*, sterile products, water, C&Q, oral solid dosage, and clinical materials

Dublin Classroom Training
Fall 2009, Dublin, Ireland

Water, *GAMP 5*, Q7A, Basic C&Q, biopharmaceutical manufacturing processes, and PAT

ISPE 2009 Annual Meeting
8-11 November 2009, San Diego, California, USA

Nine session tracks: product development, facilities and equipment, information systems, supply chain management, production systems, regulatory compliance, quality systems, project management, and investigational products

This article presents a fundamental understanding and practical application of bacterial adhesion, the first step leading to infections. This article specially focuses on two cases, cranberries and urinary tract infections, and implanted biomaterial infections.

Fundamentals of Bacterial Adhesion Applied Toward Infection Prevention: Focus on Two Case Studies

by Yatao Liu, Paola A. Pinzon-Arango, Joshua Strauss, and Terri A. Camesano

First presented by Yatao Liu at the 2007 ISPE Boston Chapter Student Poster Competition where he won the Graduate Level award, this research was then presented at the ISPE International Student Poster Competition in Las Vegas, NV later that year.

Introduction

Bacterial infections persist as a public threat due to the ease by which bacteria adapt to commonly used antibiotics. Traditional antibiotics are effective against multiplying bacteria that are planktonic (free floating). However, bacteria on surfaces develop protective communities called biofilms that hinder the ability of antibiotics to completely eliminate the pathogens. The rapid development of bacterial resistance to antibiotics has made pharmaceutical companies reluctant to fund new antibiotics research. Hence, novel approaches to prevent and treat infections are needed. One promising strategy is to control the first step of bacterial adhesion, thus preventing infection. Our work combines experiments and modeling aimed at understanding the initial steps of the bacterial adhesion process, focusing on two case studies: 1) mechanisms by which cranberry can prevent urinary tract infections through interfering with bacterial adhesion; and 2) design of anti-adhesive and antimicrobial coatings for biomaterials. We make direct adhesion force measurements between bacteria and substrates with an Atomic Force Microscope (AFM), and combine such experiments with thermodynamic calculations to develop a set of tools that allows for the prediction of whether bacteria will attach to a given surface. These fundamental investigations of the bacterial adhesion process help elucidate the underlying mechanisms behind bacterial adhesion, thus leading to improved clinical outcomes for a number of biomedical applications.

Bacterial Adhesion is the First Step in Infection Development

As one of the earliest life forms, bacteria have evolved into many thousands of species and can survive in a wide range of environments. According to National Institutes of Health (NIH), fewer than one percent of bacterial species can cause disease with most bacteria being harmless or even beneficial to humans, such as bacteria residing in human intestines that help digest food[1] or cultures that contribute to the fermentation processes of yogurts and cheeses. Despite the fact that most bacteria are not pathogens, infectious diseases claim 1,500 deaths per hour worldwide.[2] Bacterial infections that lead to pneumonia, tuberculosis, and severe diarrheal diseases, along with infectious agents of malaria, measles, and HIV/AIDS, account for half of all premature deaths worldwide, especially affecting children and young adults.[2] Due to antibiotic resistance, some infections cannot be cured by conventionally prescribed antibiotics. For example, nearly 19,000 people died in the United States in 2005 after being infected with methicillin-resistant *Staphylococcus aureus* strains that have spread rampantly through hospitals and long term care facilities.[3]

The increasing public health crisis caused by bacterial resistance necessitates alternative approaches to preventing and curing infections. The initiation of a bacterial infection requires that bacteria first attach to host tissue. The attachment of bacteria to a surface is typically described as occurring through two stages: long range, non-specific forces help the bacterium make a close contact with host cells or a substratum, where stronger specific forces can become operative. Once attached, bacteria grow, secrete extracellular material, and can develop a biofilm, which is a dense and protective community of microorganisms.

The initial adhesion process is considered to be governed by specific and non-specific inter-

action forces between bacteria and substrata. Non-specific interactions typically refer to 1. Lifshitz-van der Waals (LW) forces that are almost always attractive and operate between any two bodies 2. electrostatic interactions, which are often repulsive because bacteria and many surfaces each possess negative charges, and 3. electron-donor/electron-acceptor or Lewis Acid/Base (AB) forces, which include hydrogen bonding. Specific forces, which are much stronger, refer to bonds between ligands and receptors of two biological samples. We discuss our approach to modeling and measuring the forces involved in the initial bacterial adhesion process.

Methods in Studying Bacterial Adhesion

Bacterial adhesion can be studied at various scales, from macroscale studies that show the adhesion behavior of a population of bacteria, to nanoscale studies that probe individual cells or molecules associated with bacteria. Although macroscale studies are phenomena-oriented, they cannot provide information needed to disclose the underlying mechanisms. A combination of studies at different length scales can provide a more detailed picture.

Direct Force Measurements

Interaction forces between bacteria and host cells or implanted medical devices directly determine whether bacteria will adhere. Although the quantification of adhesion forces between bacteria and a substrate represents the most accurate and straightforward way of gaining information on bacterial adhesion, in practice, there are two crucial issues that need addressing.

Tiny Forces

The interaction forces between bacteria and a substrate are very small with values typically at the pico-Newton (pN) to nano-Newton (nN) scales, i.e., (7-70) × 10^{-12} lb·ft/s^2. Currently, only two techniques can be used to directly detect such forces. One is optical tweezers[4] and the other is atomic force microscopy (AFM).[5, 6, 7] AFM provides larger measurement range and more sophisticated controls, such as the loading rate, in addition to providing simultaneous high resolution imaging - *Figure 1*. There are additional indirect techniques used to estimate the interaction forces. These techniques include Total Internal Reflection Microscopy (TIRM), Total Internal Reflection Aqueous Fluorescence (TIRAF) microscopy, Surface Forces Apparatus (SFA), and Quartz Crystal Microbalance with energy Dissipation (QCM-D), etc. Interested readers are encouraged to refer to a comprehensive review paper on the use of these techniques in bacterial adhesion studies.[8]

Obtaining Correct Orientations of Biological Molecules

In order for bacterial ligands to correctly bind with receptors, the molecules on bacterial surfaces, including fimbriae (pili),

Continued on page 58.

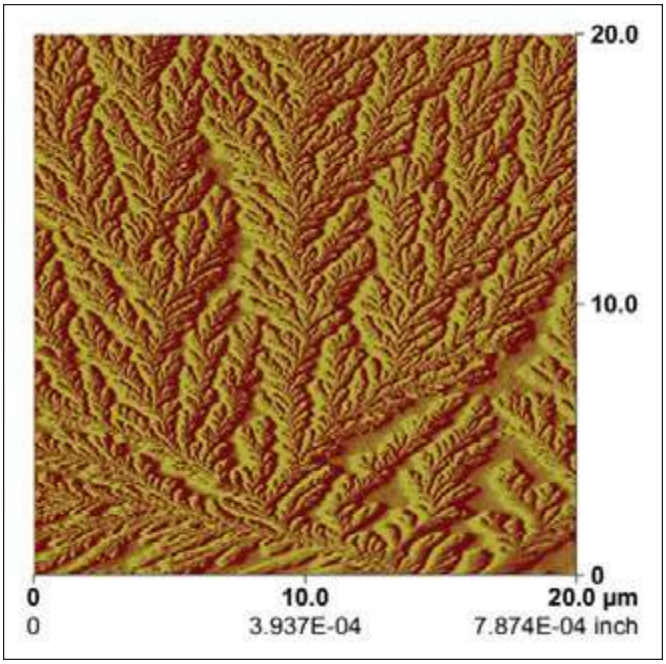


Figure 1. Representative AFM amplitude imaging of the deposition of *E. coli* culture solution after washed three times with phosphate buffer saline. Then the solution was deposited onto a mica surface. They formed a tree-like crystallization.

and lipopolysaccharides, must expose the appropriate orientation. Experimentally, it is challenging to maintain correct orientation when biological cells are trapped in optical tweezers or immobilized on an AFM tip. In our lab, we invented a novel coating method that can be used to attach bacteria to an AFM tip (Figure 2), such that they possess the correct orientation for direct force measurements.[9]

Some technical issues also need to be resolved in force measurements such as the timescale and loading rate. The timescale needed to build a ligand-receptor bond can be difficult to determine. Further, the loading rate needed to make AFM force measurements has to be specified for each experiment. These parameters should be appropriately determined to obtain correct force measurements.

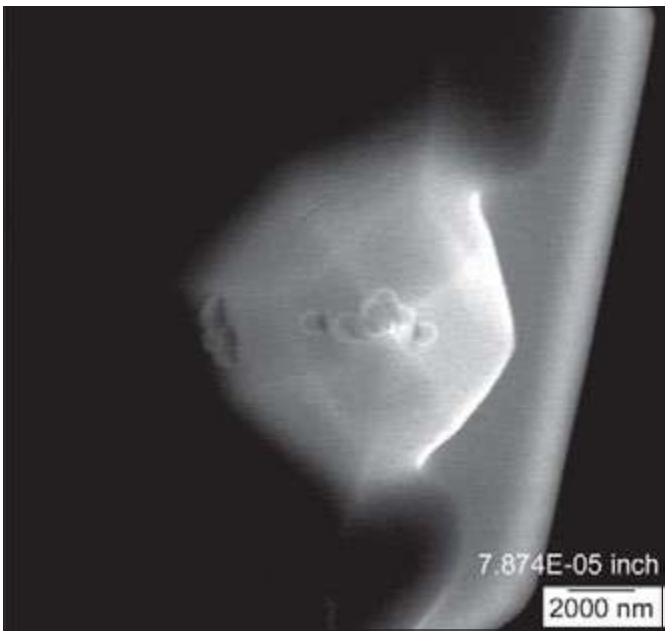


Figure 2. Representative SEM imaging of *S. epidermidis* coated AFM tip.

Thermodynamic Modeling of Bacterial-Surface Interactions

Classical and extended Derjaguin-Landau-Verwey-Overbeek (DLVO) theory has been used to explain and predict the adhesion behavior of bacteria in aqueous media. The DLVO model takes into account van der Waals interactions, electrostatic interactions, and often includes electron donor/electron acceptor interactions when the extended DLVO model is applied. Parameters to include in the thermodynamic models need to be estimated for each bacterium, substrate, and solution. For example, zeta potential measurements on bacteria in a suspension are used for the modeling of electrostatic interactions.

Parameters for the thermodynamic calculations are taken from contact angle measurements on bacterial lawns and on the substrates of interest, using probe liquids with varying polarities. Individual surface tensions can be calculated from the measured contact angles by using the Young-Dupré equation.[10] The Gibbs free energy change due to adhesion is calculated from the interfacial tensions for bacteria/substrate, bacteria/water, and substrate/water. If bacteria can attach to a substrate, then the newly formed interface (bacteria-substrate) must be more stable than the two old interfaces (substrate-liquid and bacteria-liquid). The Gibbs free energy change during the process must be negative to favor the new interface, which represents bacteria attached to the substrata. If the Gibbs free energy change is positive, bacteria prefer to not attach to the surface, but to remain in the aqueous media. One advantage for using thermodynamic modeling is that the method is reliable for many kinds of substrates, especially when at least one non-biological surface is applied. In addition, this method has a strong and well-defined theoretical foundation, which helps to fundamentally explain bacterial adhesion and offer a theoretical guide for biomaterial development or infection-prevention strategy. However, the thermodynamic modeling only accounts for non-specific interactions. If both surfaces are biological samples, ligand-receptor interactions may be present. Then the interaction forces calculated from the thermodynamic model will be greatly underestimated, as we reported earlier.[11] A detailed explanation on the use of these models for bacterial adhesion calculations was reported in our previous studies.[11]

Macroscale Studies of Bacterial Attachment

One of the simplest ways to quantify bacterial attachment to a surface is via a retention assay. Bacteria are incubated with host cells or the biomaterial of interest; either statically or under flow conditions. After a pre-determined time, host cells or the substrata are removed and washed to remove the loosely attached bacteria. The percentage of attached bacteria that are viable can be quantified using a dual DNA staining kit, in which green and red fluorochromes can be used to discern the number of viable cells - *Figure 3*.

Although a bacterial retention assay is a quick way to screen various surfaces or treatments, it does not provide mechanistic information on why bacteria attach. In addition, it can be difficult to conduct the experiments reproducibly, particularly if bacteria aggregate, making it difficult to get accurate cell counts. Numerous trials may be required to obtain statistically meaningful data. However, this simple assay may be used as a reference method to compare with other methods of quantifying bacterial adhesion.

Case Studies

While there are numerous types of bacterial infections with varying degrees of clinical severity, we focus on two examples that our lab has studied extensively.

Case I: Cranberry as a Preventive Measure for Urinary Tract Infections (UTIs)

UTIs and Antibiotic Resistance

Urinary tract infections are defined as infections of the kidneys, ureters, bladder, or urethra and are the second most common type of infection in the US. Symptoms generally include a frequent urge to urinate, pain and burning in the area of the bladder or urethra during urination, and in some cases, fever, fatigue, and trembling. Women, infants, and elders are more prone to UTIs. Approximately one third of women will have at least one UTI in their lifetime.[12] The annual rate of infection among women in the United States is 11.3 million symptomatic cases[13] and more than 10 million asymptomatic cases.[14] The estimated annual medical expenditures are more than $1.6 billion.[15] The Gram-negative bacterium *Escherichia coli* is the main culprit, responsible for 85 to 95 percent of cystitis cases (bladder infection) and 90 percent of acute pyelonephritis cases (a serious kidney infection).[16]

Although most bacterial infections are treatable with antibiotics, bacterial resistance to currently available antibiotics has become an increasing threat to public health, largely due to inappropriate dosing and administration of antibiotics, as well as the rapid ability of bacteria to exchange genetic information that confers resistance. Cotrimoxazole (trimethoprim/sulfamethoxazole) is the current first-line treatment for uncomplicated UTIs in the US and many other countries, but cotrimoxazole resistance exceeds 15 percent and can be as high as 25 percent in Canada and the US.[17]

Cranberries and UTIs

Native Americans used cranberries as a food source, and for many years, cranberries have been experientially recognized for their benefits of maintaining urinary tract health. Preliminary clinical studies of cranberry's benefits began in the early 1920s.[18, 19] In 1994, Avorn et al. were the first to successfully demonstrate that consumption of cranberry juice reduces the frequency of recurrent urinary tract infections in a population of elderly women. Although very early studies

Continued on page 60.

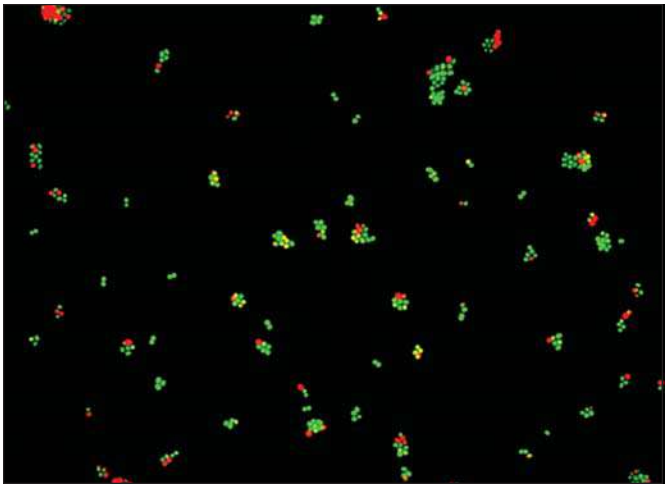


Figure 3. Representative image of *S. epidermidis* stained with live/dead kit for an adhesion assay.

hypothesized that increased acidity produced in the urine by eating cranberries was the reason for the beneficial effect,[18] more recent work has shown that the pH of urine after cranberry juice cocktail consumption only changes slightly[20] and is transient.[21]

In 1984, Sotoba et al. found that preincubation of *E. coli* and uroepithelial cells in cranberry juice decreased bacterial adhesion,[22] leading to a paradigm shift in the understanding of the action of cranberry on bacterial adhesion. Since that time, researchers have focused their efforts on gaining a detailed molecular-scale understanding of the mechanisms behind this action.

Molecular Mechanisms of Cranberries Preventing UTIs

Compounds in cranberries affect molecules on the surface of Gram-negative bacteria. For example, fimbriae are proteinaceous structures that extend from *E. coli* and contain a specific adhesin molecule (PapG) that helps the bacteria bind to a receptor on uroepithelial cells, known as the α-Gal(1→4)β-Gal oligosaccharide receptor. *E. coli* that posses P type fimbriae can cause more serious types of UTIs, such as acute kidney infection (pyelonephritis), in addition to the less severe cystitis (bladder infection). We review some of our recent work, focusing on P-fimbriated *E. coli* and a non-fimbriated mutant strain, which allowed us to better understand the role of cranberry compounds on P fimbriae.

Bacterial Retention Assay

Building upon the available clinical studies, we performed *in vitro* bacterial adhesion assays that were designed to help understand the mechanisms behind cranberry's action on the *E. coli*-uroepithelial cell interaction. Using neutralized cranberry juice so that the effects of pH on bacterial adhesion could be eliminated, we found that the number of attached *E. coli* per uroepithelial cells decreased from 50.2 ± 22.9 bacteria/uroepithelial cell without cranberry juice treatment, to 13.6 ± 5.7, 9.3 ± 4.1, and 2.9 ± 1.5 bacteria/uroepithelial cell, corresponding to 5, 10, and 27 wt.% cranberry juice treatment, respectively.[23] These *in vitro* attachment results confirmed that cranberry juice cocktail can reduce bacterial attachment to host tissue, and that lower pH is not the underlying mechanism that makes cranberry juice an effective agent for preventing UTIs.

P-fimbriae Morphology Characterization

Through Atomic Force Microscopy (AFM) measurements, together with steric modeling, we found that the average P-fimbriae length on *E. coli* HB101pDC1 was 147 nm (around 600 × 10^{-8} inch) without cranberry juice treatment, but decreased to 50 nm (around 200 × 10^{-8} inch) when bacteria were exposed to cranberry juice - *Figure 4*.[24] Thus, we directly demonstrated that although P fimbriae are not removed by exposure to cranberry juice, the proteins become compressed significantly after cranberry juice treatment, which may account for their decreased ability to adhere to uroepithelial cells.

Direct Force Measurements

In addition, AFM was used to show that the adhesion force between *E. coli* and a uroepithelial cell was ~10 nN (7.233 × 10^{-8} lb·ft/s^2) when no cranberry juice cocktail was present, but decreased to ~0.50 nN (0.362 × 10^{-8} lb·ft/s^2) after cells were exposed to 27% cranberry juice cocktail.[25] The specific adhesion forces between PapG adhesin and receptors on uroepithelial cells were significantly decreased after cranberry juice treatment. This was the first study to directly demonstrate that cranberry juice treatment reduces the nanoscale adhesion forces between bacteria and uroepithelial cells.

Thermodynamic Modeling

Through thermodynamic modeling, we showed that the Gibbs free energy change (ΔG_{adh}) between *E. coli* and uroepithelial cells in the absence of cranberry juice treatment was -20 mJ/m^2 (around -150 ft-lbs/ft^2), where the negative value implies that bacterial adhesion is favorable. With increasing concen-

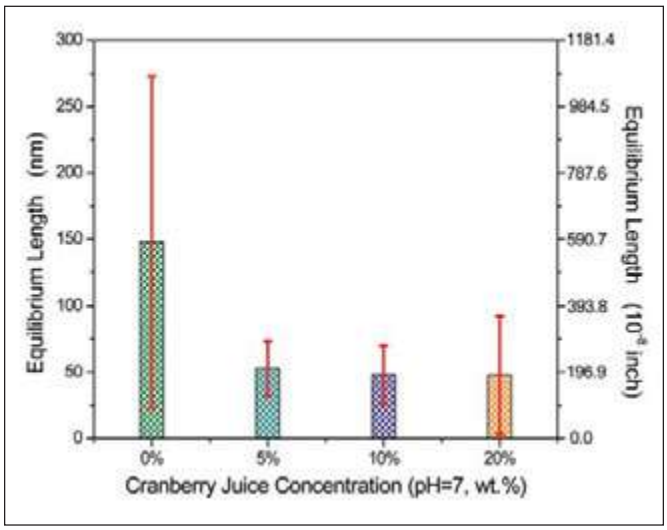


Figure 4. The average equilibrium length of P fimbriae on *E. coli* surface derived from steric modelling based on AFM surface characterizations. Adapted with permission from Liu *et al.*, *Biotechnology and Bioengineering*, 2006, **93**, 301 (Ref. 24). Copyright (2005) Wiley Periodicals, Inc.

trations of cranberry juice treatment, increased and became positive when the bacteria and uroepithelial cells were exposed to at least 20 wt. percent cranberry juice cocktail, suggesting that at or above this concentration, bacterial adhesion is unfavorable.[26] These results imply that cranberry juice can impair non-specific interactions between bacteria and uroepithelial cells and hence prevent bacterial adhesion.

Therefore, cranberry can provide protection at three different levels:

a. Cranberry juice exposure compresses P fimbriae of *E. coli*, thus preventing adhesion between the bacterium and the uroepithelial cell.

b. Cranberry juice increases the repulsive energy barrier to adhesion, over a range of hundreds of nanometers (400 × 10^{-8} inch), thus preventing the bacteria from coming into contact with the uroepithelial cells.

c. Even if bacteria are able to penetrate the repulsive energy barrier, the action of cranberry juice on the bacteria decreases the ability of the bacteria to attach to uroepithelial cells, as demonstrated through direct force measurements.

Future Directions for Cranberry Research

Although progress has been made in understanding cranberry's actions against *E. coli* toward the protection of urinary tract health, there are a number of key research issues that remain to be addressed. For example, a large body of research is devoted to identifying the critical compounds in cranberry that cause the anti-adhesive benefits, and in elucidating the needed dose and duration of exposure to such compounds. Due to the acidity of cranberry juice, commercially available cranberry juice cocktails are sweetened with fructose, water, and vitamin C, yielding 25 to 27 wt. percent cranberry juice. Therefore, there are more than 120 different compounds in cranberry juice.[27] Most research has focused on isolating and identifying the class of A-type proanthocyanidins (PACs) or non-dialyzable materials, which have shown decreases in bacterial adhesion *in vitro*.[28, 29, 30, 31, 32, 33]

However, it is not easy to translate the dose required to impart an anti-adhesion effect in an *in vitro* study to the dose needed for clinical relevance. Our *in vitro* studies showed that 5.0 wt. percent cranberry juice was sufficient to prevent bacterial adhesion[24, 25] from the molecular scale perspective for the first time although similar results were observed in prior *in vitro* bacterial adhesion assay experiments.[30, 34] Although it is not yet known how these *in vitro* thresholds will translate to *in vivo* conditions, researchers are actively engaged in trying to extend laboratory-scale mechanistic studies toward clinical trials. Increased understanding of the molecular action of cranberry juice on *E. coli* and uroepithelial cells can lead to better estimation of needed cranberry juice dose and duration.

Continued on page 62.

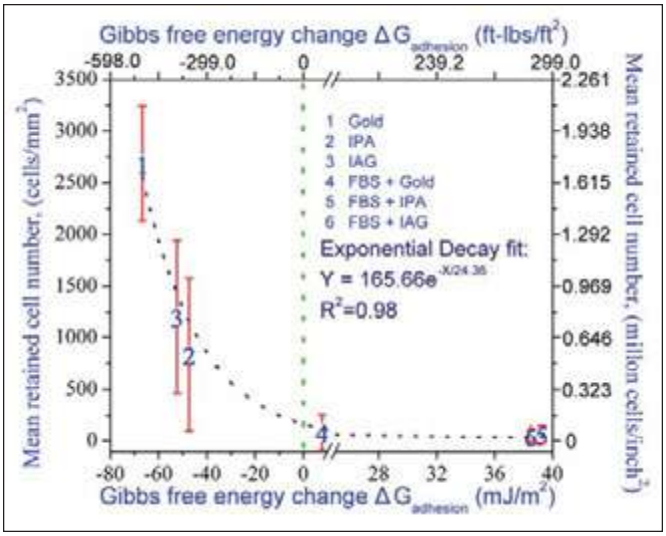


Figure 5. Correlation between Gibbs free energy change and *S. epidermidis* retention. Adapted with permission from Liu *et al.*, *Langmuir*, 2007, **23**, 7138 (Ref. 11). Copyright (2007) American Chemical Society.

Case II: Infections of Implanted Medical Devices

Infections on Biomaterials

Modern medicine is highly dependent on implanted medical devices, such as catheters, cerebrospinal fluid shunts, prosthetic heart valves and prosthetic joints, vascular grafts, cardiac pacemakers, and intraocular lenses, etc., which have significantly improved quality of treatments for patients. However, any time a foreign material is introduced into the body; this surface becomes a likely site of bacterial infection. For example, 4.3 percent of 2.6 million orthopedic implants and 7.4 percent of cardiovascular implants become infected per year.[35, 36] Bacterial infections occur in more than two million surgical cases each year in the US alone, which burdens patients both physically and financially.[37] Annually in the US, there are more than 250,000 Catheter Related Bloodstream Infections (CRBSIs).[38] The Gram-positive bacterium *Staphylococcus epidermidis* has evolved as a leading cause of nosocomial sepsis and is the most frequently isolated causal organism for infections of numerous types of catheters, shunts, and other implanted medical devices.[39, 40, 41] For example, *S. epidermidis* and other coagulase-negative *Staphylococci* were the causal agents in ~50 percent of CRBSIs.[42]

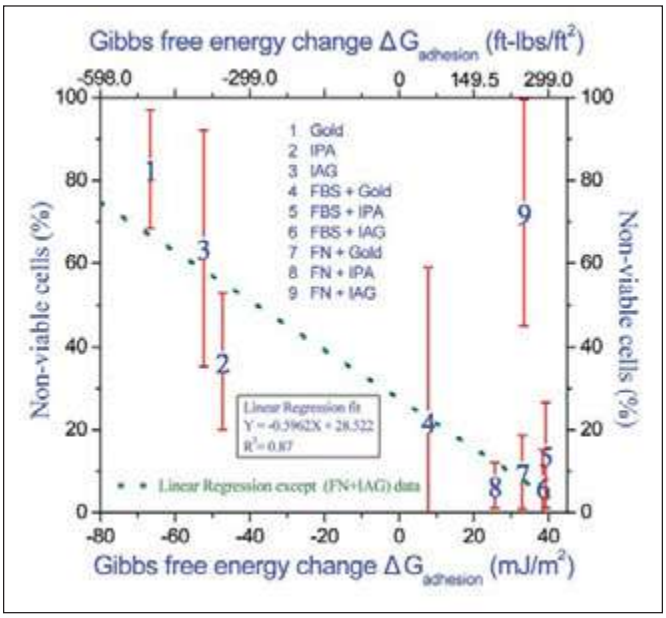


Figure 6. Correlation between Gibbs free energy change and *S. epidermidis* viability. Adapted with permission from Liu *et al.*, *Langmuir*, 2007, **23**, 7138 (Ref. 11). Copyright (2007) American Chemical Society.

Once bacteria attach to implanted medical devices, they can easily form a protective biofilm because the biofilm community is encased in a matrix of polysaccharides and proteins, which presents a diffusion barrier for antimicrobial agents' penetration. Further, the reduced metabolic rate of the bacteria in the biofilm causes a slow rate of uptake of antimicrobial agents. The biofilm also shields bacteria from environmental stresses.[43] Often the only effective treatment of an infected implanted medical device is surgical excision.[44] In addition to increasing the patient's morbidity, mortality, and recovery time, the economic expenditure on bacterial-infected medical devices exceeds $3 billion per year in the US alone.[35]

Strategies toward Preventing Implanted Medical Device Related Infections

Current research is focused on designing materials that resist bacterial adhesion or that inactivate attached bacteria. One strategy has been to coat antimicrobial agents directly onto the implanted materials to kill bacteria upon initial adhesion or as they begin to grow. A variety of antibiotics such as vancomycin, gentamicin, clindamycin, fusidic acid, ciprofloxacin, cefuroxime, cefotaxime, and chlorhexidine have been tested *in vitro* and in animal models;[45, 46, 47] however, only limited success has been obtained. The main challenge is that it is difficult to maintain a steady release of drug from the biomaterial. The focus of several research groups, including ours, is to develop materials that resist the adhesion of bacteria to surfaces. Coatings such as Self-Assembled Monolayers (SAMs) and polymers have demonstrated the ability to prevent bacterial adhesion by modifying surface properties such as hydrophobicity, roughness, and surface charge.[7, 48, 49] However, bacterial adhesion results do not show consistent trends in terms of the physicochemical properties of the surfaces. For example, we showed that surface wettability and roughness were insufficient properties to correlate with bacterial adhesion.[7] A better ability to characterize the properties of biomaterials at the molecular level may lead to better design of antibacterial biomaterials.

Use of Self-Assembled Monolayers (SAMs) to Create Anti-Adhesive Coatings

SAMs possess a layer of molecules with the same terminal group and uniform orientation, properties that facilitate the study of bacterial adhesion since bacteria are always exposed to the same chemical groups. In our laboratory, we developed a series of SAMs with varying terminal groups that were designed to resist bacterial adhesion and/or inactivate bacteria. The two most promising candidates we identified were

dodecanethiol-based SAMs (terminating in isophthalic acid or isophthalic acid with silver). The silver-containing SAMs were of interest because the antibacterial properties of silver have been demonstrated, and bacteria are unable to develop a resistance to silver's antimicrobial abilities.[50] In addition, silver has been shown to be nontoxic to mammalian cells at similar concentrations.[51]

When evaluating the potential of an antibacterial coating for a particular biomaterial, it is also important to consider how serum and plasma proteins, such as fibronectin, laminin, fibrin, and albumin will adsorb to the biomaterial. In our work, we also tested the adsorption of model proteins (fetal bovine serum and fibronectin) to the SAM-coated materials.

We found that the attachment of *S. epidermidis* to the protein-coated material depended on the particular protein present. Fetal bovine serum adsorption reduced the attachment of *S. epidermidis* to the material, while fibronectin coating promoted *S. epidermidis* attachment.[52]

SAMs terminating in Isophthalic Acid (IPA) and Isophthalic Acid with silver (IAG) resulted in lower non-specific adhesion forces with *S. epidermidis* compared to bare surfaces, as supported by thermodynamic modeling. When serum proteins were adsorbed on the SAMs, non-specific interactions between the bacteria and substrate decreased - *Figure 5*. While the LW forces were unchanged, AB forces were found to dominate the overall interaction, and showed more variability in terms of the type of SAM and protein put on the substrate. Since AB forces mainly reflect hydrogen bonds, we suggest that a fruitful approach to enhanced development of antimicrobial biomaterials would be to select materials that prevent or limit the formation of hydrogen bonds.[11]

The thermodynamic modeling was supported by direct AFM force measurements between an *S. epidermidis*-coated AFM tip and the various SAMs or protein-coated surfaces. Stronger adhesion forces were observed between *S. epidermidis* and fibronectin than between the bacteria and fetal bovine serum, due to the formation of strong ligand-receptor bonds that can only occur with fibronectin.[53] Since protein coatings can mask the underlying surface properties, it is important to consider the competition between *S. epidermis* and serum protein for adsorption to the biomaterial.

In our study, the IPA-terminating SAM showed the best activity in terms of preventing bacterial adhesion and inactivating bacteria. IAG showed strong anti-bacterial adhesion properties similar to IPA. In addition, IAG killed around 60 percent attached *S. epidermidis*[11] - *Figure 6*. IAG coated with a protein layer of more than 100 nm (3.94×10^{-6} inch) still was able to present antibacterial activity since we assume some silver ions could diffuse through the protein layer. However, when the protein coating was thicker than 250 nm (9.85×10^{-6} inch), the ability of the SAM to inactivated bacteria decreased significantly.[52] These results emphasize again that bio-

Continued on page 64.

material development studies need to consider the interactions of materials with *in vivo* proteins, as well as with bacterial pathogens.

Conclusions

As a crucial step leading to infection development, the creation of new tools to experimentally measure and model bacterial adhesion can lead to health benefits. In particular, we discussed how atomic force microscopy and thermodynamic modeling could be used to study the fundamental adhesion processes related to urinary tract infections and bacterial infections on biomaterials.

References

1. Van Loo, J. and Jonkers, N., "Evaluation in Human Volunteers of the Potential Anticarcinogenic Activities of Novel Nutritional Concepts: Prebiotics, Probiotics and Synbiotics," *Nutrition, Metabolism, and Cardiovascular Diseases,* Vol. 11, No. 4, 2001, pp. 87-93.
2. WHO Report in World Health Organization Report on Infectious Diseases, World Health Organization, Geneva, Switzerland, 1999.
3. Klevens, R.M., Morrison Melissa, A., and Nadle, J., *et al.*, "Invasive Methicillin-Resistant *Staphylococcus aureus* Infections in the United States," *The Journal of the American Medical Association,* Vol. 298, No. 15, 2007, pp. 1763-71.
4. Jass, J., Schedin, S., Fallman, E., *et al.*, "Physical Properties of *Escherichia coli* P pili Measured by Optical Tweezers," *Biophysical Journal,* Vol. 87, No. 6, 2004, pp. 4271-83.
5. Abu-Lail, L.I., Liu, Y., Atabek, A., and Camesano, T.A., "Quantifying the Adhesion and Interaction Forces Between *Pseudomonas aeruginosa* and Natural Organic Matter," *Environmental Science and Technology,* Vol. 41, No. 23, 2007, pp. 8031-8037.
6. Liu, Y., Gallardo-Moreno, A.M. and Camesano, T.A. Abstracts of Papers, 106 ASM General Meeting, Orlando, Florida, United States, 20-24 May 2006.
7. Emerson, R.J., IV, Bergstrom, T.S., Liu, Y., et al., "Microscale Correlation between Surface Chemistry, Texture, and the Adhesive Strength of *Staphylococcus epidermidis*," *Langmuir,* Vol. 22, No. 26, 2006, pp. 11311-11321.
8. Camesano, T.A., Liu, Y., and Datta, M., "Measuring Bacterial Adhesion at Environmental Interfaces with Single-Cell and Single-Molecule Techniques," *Advances in Water Resources,* Vol. 30, No. 6-7, 2007, pp. 1470-1491.
9. Camesano, T.A., Liu, Y., and Gallardo-Moreno, A., (Worcester Polytechnic Institute, USA), PCT International Patent Application, pp. 47, WO 2007109689, 2007.
10. Van Oss, C. J., Interfacial Forces in Aqueous Media. Dekker, New York, New York, 1994
11. Liu, Y., Strauss, J., and Camesano, T.A., "Thermodynamic Investigation of *Staphylococcus epidermidis* Interactions with Protein-Coated Substrata," *Langmuir,* Vol. 23, No. 13, 2007, pp. 7134-7142.
12. Sobel, J.D., "Bacterial Etiologic Agents in the Pathogenesis of Urinary Tract Infection," *The Medical Clinics of North America,* Vol. 75, No. 2, 1991, pp. 253-273.
13. Foxman, B., Barlow, R., D'Arcy, *et al.*, "Urinary Tract Infection: Self-Reported Incidence and Associated Costs," *Annals of Epidemiology,* Vol. 10, No. 8, 2000, pp. 509-515.
14. Reid, G., "Applications from Bacterial Adhesion and Biofilm Studies in Relation to Urogenital Tissues and Biomaterials: A Review," *Journal of Industrial Microbiology,* Vol. 13, No. 2, 1994, pp. 90-96.
15. Foxman, B., "Epidemiology of Urinary Tract Infections: Incidence, Morbidity, and Economic Costs," *The American Journal of Medicine,* Vol. 113, Suppl. 1A, 2002, pp. 5S-13S.
16. Russo Thomas, A. and Johnson James, R., "Medical and Economic Impact of Extraintestinal Infections due to *Escherichia coli*: Focus on an Increasingly Important Endemic Problem," *Microbes and Infection / Institute Pasteur,* Vol. 5, No. 5, 2003, pp. 449-56.
17. Blondeau, J.M., "Current Issues in the Management of Urinary Tract Infections: Extended-Release ciprofloxacin as a Novel Treatment Option," *Drugs,* Vol. 64, No. 6, 2004, pp. 611-628.
18. Blatherwick, N.R. and Long, M.L., "Studies of Urinary Acidity. II. The Increased Acidity Produced by Eating Prunes and Cranberries," *Journal of Biological Chemistry,* Vol. 57, 1923, pp. 815-818.
19. Blatherwick, N.R., "The Specific Role of Foods in Relation to the Composition of the Urine," *Archives of Internal Medicine,* Vol. 14, 1914, pp. 409-450.
20. Bodel, P.T., Cotran, R., and Kass, E.H., "Cranberry Juice and the Antibacterial Action of Hippuric Acid," *Journal of Laboratory and Clinical Medicine,* Vol. 54, 1959, pp. 881-888.
21. Walsh, B.A., "Urostomy and Urinary pH," *Journal of ET nursing,* Vol. 19, No. 4, 1992, pp. 110-113.
22. Sobota, A.E., "Inhibition of Bacterial Adherence by Cranberry Juice: Potential Use for the Treatment of Urinary Tract Infections," *The Journal of Urology,* Vol. 131, No. 5, 1984, pp. 1013-1016.
23. Pinzon-Arango, P.A., Liu, Y., and Camesano, T.A., (2007) Abstracts of Papers, 234th ACS National Meeting, Boston, Massachusetts, United States, 19-23 August 2007.
24. Liu, Y., Black, M.A., Caron, L., and Camesano, T.A., "Role of Cranberry Juice on Molecular-scale Surface Characteristics and Adhesion Behavior of *Escherichia coli*," *Biotechnology and Bioengineering,* Vol. 93, No. 2, 2006, pp. 297-305.
25. Camesano, T.A., Liu, Y., and Pinzon-Arango, P.A., "Cranberry Prevents the Adhesion of Bacteria: Overview of Relevant Health Benefits," *AgroFOOD Industry Hi-Tech,* Vol. 18, No. 1, 2007, pp. 24-27.
26. Liu, Y., Gallardo-Moreno, A.M., and Camesano, T.A., (2006) Abstracts of Papers, 232nd ACS National Meeting, San Francisco, California, United States, 10-14 September 2006.
27. Shahidi, F., Weerasinghe, D.K., and Editors, ACS Symposium Book: Nutraceutical Beverages: Chemistry, Nutrition, and Health Effects, American Chemical Society, Washington, DC, 2004.
28. Howell, A.B., "Cranberry Proanthocyanidins and the Maintenance of Urinary Tract Health," *Critical Reviews in Food*

Science and Nutrition, Vol. 42, No. 2 Suppl., 2002, pp. 273-278.
29. Howell, A.B.V., Nicholi, (2003), "Plant Proanthocyanidin Extract Effective at Inhibiting Adherence of Bacteria with P-type Fimbriae to Surfaces," U.S. Patent 6608102, 2003, pp. 24.
30. Howell, A.B., Reed, J.D., Krueger, C.G., *et al*., "A-type Cranberry Proanthocyanidins and Uropathogenic Bacterial Anti-Adhesion Activity," *Phytochemistry*, Vol. 66, No. 18, 2005, pp. 2281-2291.
31. Howell, A.B., "Bioactive Compounds in Cranberries and their Role in Prevention of Urinary Tract Infections," *Molecular Nutrition and Food Research*, Vol. 51, No. 6, 2007, pp. 732-737.
32. Zafriri, D., Ofek, I., and Adar, R., *et al*., "Inhibitory Activity of Cranberry Juice on Adherence of Type 1 and Type P Fimbriated *Escherichia coli* to Eucaryotic Cells," *Antimicrobial Agents and Chemotherapy*, Vol. 33, No. 1, 1989, pp. 92-98.
33. Steinberg, D., Feldman, M., Ofek, I., and Weiss, E.I., "Effect of a High-Molecular-Weight Component of Cranberry on Constituents of Dental Biofilm," *Journal of Antimicrobial Chemotherapy*, Vol. 54, No. 1, 2004, pp. 86-89.
34. Burger, O., Ofek, I., and Tabak, M., et al., "A High Molecular Mass Constituent of Cranberry Juice Inhibits Helicobacter Pylori Adhesion to Human Gastric Mucus," *FEMS Immunology and Medical Microbiology*, Vol. 29, No. 4, 2000, pp. 295-301.
35. Darouiche, R.O., "Treatment of Infections Associated with Surgical Implants," *New England Journal of Medicine*, Vol. 350, No. 14, 2004, pp. 1422-1429.
36. Hetrick, E.M. and Schoenfisch, M.H., "Reducing Implant-Related Infections: Active Release Strategies," *Chemical Society Reviews*, Vol. 35, No. 9, pp. 780-789.
37. Correa, L. and Pittet, D., "Problems and Solutions in Hospital-Acquired Bacteraemia," *The Journal of Hospital Infection*, Vol. 46, No. 2, 2000, pp. 89-95.
38. Raad, I., "Intravascular-Catheter-Related Infections," *Lancet*, Vol. 351, No. 9106, 1998, pp. 893-8.
39. Kloos, W., **Taxonomy and Systematics of *Staphylococci* Indigenous to Humans,** Churchill Livingstone, New York, 1997.
40. Noble, W., ***Staphylococcal* Carriage and Skin and Soft Tissue Infection,** Churchill Livingstone, New York, 1997.
41. Mack, D., "Molecular Mechanisms of *Staphylococcus epidermidis* Biofilm Formation," *The Journal of Hospital Infection*, Vol. 43, 1999, pp. S113-S125.
42. Blot Stijn, I., Depuydt, P., and Annemans, L., *et al*., "Clinical and Economic Outcomes in Critically Ill Patients with Nosocomial Catheter-related Bloodstream Infections," *Clinical Infectious Diseases*, Vol. 41, No. 11, 2005, pp. 1591-1598.
43. Francolini, I., Donelli, G., and Stoodley, P., "Polymer Designs to Control Biofilm Growth on Medical Devices," *Reviews in Environmental Science and Bio/Technology*, Vol. 2, No. 2-4, 2004, pp. 307-319.
44. Gristina, A.G., "Biomaterial-centered Infection: Microbial Adhesion versus Tissue Integration," *Science*, Vol. 237, No. 4822, 1987, pp. 1588-1595.
45. Sherertz, R.J., Forman, D.M., and Solomon, D.D., "Efficacy of Dicloxacillin-coated Polyurethane Catheters in Preventing Subcutaneous Staphylococcus Aureus Infection in Mice," *Antimicrobial Agents and Chemotherapy*, Vol. 33, No. 8, 1989, pp. 1174-1178.
46. Stigter, M., Bezemer, J., de Groot, K., and Layrolle, P., "Incorporation of Different Antibiotics into Carbonated Hydroxyapatite Coatings on Titanium Implants, Release and Antibiotic Efficacy," *Journal of Controlled Release*, Vol. 99, No. 1, 2004, pp. 127-137.
47. Price, J.S., Tencer, A.F., Arm, D.M., and Bohach, G.A., "Controlled Release of Antibiotics from Coated Orthopedic Implants," *Journal of Biomedical Materials Research*, Vol. 30, No. 3, 1996, pp. 281-286.
48. Ista, L.K., Fan, H.Y., Baca, O., and Lopez, G.P., "Attachment of Bacteria to Model Solid Surfaces: Oligo (Ethylene Glycol) Surfaces Inhibit Bacterial Attachment," *Fems Microbiology Letters*, Vol. 142, No. 1, 1996, pp. 59-63.
49. Chapman, R.G., Ostuni, E., and Liang, M.N., et al., "Polymeric Thin Films that Resist the Adsorption of Proteins and the Adhesion of Bacteria," *Langmuir*, Vol. 17, No. 4, 2001, pp. 1225-1233.
50. Lee, S. and Voeroes, J., "An Aqueous-Based Surface Modification of Poly (dimethylsiloxane) with Poly (ethylene glycol) to Prevent Biofouling," *Langmuir*, Vol. 21, No.

Concludes on page 66.

25, 2005, pp. 11957-11962.
51. Bologna, R.A., Tu, L.M., and Polansky, M., *et al.*, "Hydrogel/Silver ion-coated Urinary Catheter Reduces Nosocomial Urinary Tract Infection Rates in Intensive Care Unit Patients: A Multicenter Study," *Urology*, Vol. 54, No. 6, 1999, pp. 982-987.
52. Camesano, T.A. and Mello, C., ACS Symposium Book: Structure, Interactions and Reactivity at Microbial Surfaces, American Chemical Society, Washington, DC, 2008.
53. Liu, Y., Strauss, J., and Camesano, T.A., "Adhesion forces between *Staphylococcus epidermidis* and surfaces bearing self-assembled menolayers in the presence of model proteins," *Biomaterials*, Vol. 29, No. 33, 2008, pp. 4374-4382.

Acknowledgements

This work was supported in part by the National Science Foundation (BES 0238627 and EEC 0452809). Paola Pinzon-Arango received Fellowship support from the American Association for University Women.

We also thank Dr. Amparo Gallardo-Moreno, Dr. Stephen Heard, Dr. W. Grant McGimpsey, Dr. Ray Emerson, Ms. Arzu Atabek, Ms. Laila Abu-Lail, and Mr. Eftim Milkani for the help and discussions throughout the course of these studies, and Ms. Xiaoshu Dai and Professor Satya Shivkumar for their assistance with SEM measurements.

About the Authors

Yatao Liu earned his BS and MS in chemical engineering from East China University of Science and Technology, Shanghai, China in 2003. He is currently pursuing his PhD in chemical engineering at Worcester Polytechnic Institute, Massachusetts. His research involves unveiling the mechanisms of cranberries preventing urinary tract infections. He also is engaged in developing new implanted medical materials to prevent infections based on the in-depth understanding of bacterial adhesion. He received the American Institute of Chemists Award in 2007 and is the recipient of George I. Alden Fellowship. He has published more than 10 peer-reviewed research articles and holds two granted patents and two pending patents. He can be contacted by email: yataoliu@gmail.com.

Paola Pinzon-Arango graduated with a BS in chemical engineering from Worcester Polytechnic Institute (WPI) in Worcester, Massachusetts in 2005, where she conducted research on understanding the effects of cranberry juice on bacterial adhesion to bladder cells. During her undergraduate studies, she also worked with the Ecole Nationale Supérieure des Industries Chimiques, in Nancy, France, where she investigated the stabilization of oil-in-water emulsions to encapsulate lidocaine for a controlled release drug delivery system. She received her MS in biomedical engineering from WPI in 2008. Pinzon-Arango has been engaged in research aimed at understanding the mechanisms by which cranberry juice and its isolated compounds inhibit the adhesion of *E. coli* to uroepithelial cells and how cranberry modifies surface properties of bacteria. She was awarded a Selected Professions Fellowship from the American Association of University Women in 2006. She is currently a PhD candidate from the Department of Chemical Engineering at WPI. Her research interests include scanning probe microscopy, bacterial adhesion, and effects of material coatings on *in vivo* implant performance. She can be contacted by email: ppinzon@wpi.edu.

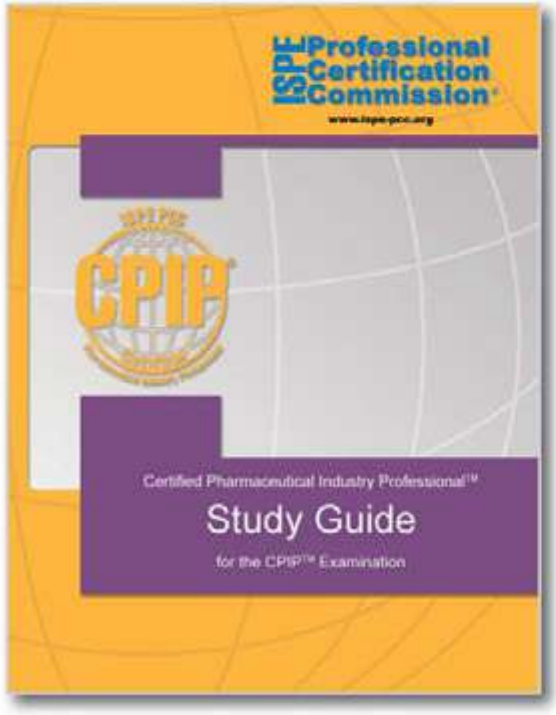
Joshua Strauss is among the first researchers to occupy Worcester Polytechnic Institute's new research facility, Life Sciences and Bioengineering Center at Gateway Park. His research encompasses the use of antimicrobial cecropins as a means to detect and eradicate pathogenic *E. coli* from food supplies. A graduate of WPI's chemical engineering program in February 2007, he is pursuing his Masters under the direction of Professor Camesano. His laboratory specializes in using equipment such as the atomic force microscope and the quartz crystal microbalance with dissipation monitoring. His work has been published in Langmuir and in two symposium book chapters with the American Chemical Society. In addition, he has presented several posters at meetings, including the American Chemical Society, the American Society for Microbiology, and the Materials Research Society. He can be contacted by email: josh1@wpi.edu.

Terri A. Camesano heads a research group in bacterial adhesion and interaction forces at Worcester Polytechnic Institute (WPI), in Worcester, Massachusetts. She received a PhD from the Pennsylvania State University in environmental engineering, an MS in environmental engineering from the University of Arizona, and a BS in chemical engineering and environmental science from the University of Rochester. She has been employed at WPI since 2000 and was named Associate Professor of Chemical Engineering in 2006. Camesano's research focuses on understanding bacterial adhesion, the initial event in biofilm formation. This work has relevance to a number of biomedical and environmental problems, such as microbial colonization of catheters and biomaterials, subsurface bioremediation, prevention of pathogenic microorganisms in drinking water, and the interactions between bacteria and host tissue in the body. Camesano is the author or co-author of more than 30 journal publications and is the recipient of an NSF CAREER Award (2003) and the Sigma Xi Junior Faculty Award for Outstanding Research (2005). She can be contacted by email: terric@wpi.edu.

Worcester Polytechnic Institute, Department of Chemical Engineering, Life Sciences and Bioengineering Center at Gateway Park, 100 Institute Rd., Worcester, Massachusetts 01609, USA.

Study Guide

Certified Pharmaceutical Industry Professional™ (CPIP™) Certification Program



A CPIP™ certification program Study Guide and CD ROM are available to assist industry professionals in enhancing their global industry knowledge and in preparing for the CPIP certification program examination.

The Study Guide provides a detailed description of nowledge elements to be included in the CPIP certification program examination. The CD ROM contains references, in the public domain, which can be used to prepare for the examination and/or as an everyday work reference tool.

Being certified to an international competency (knowledge and skills) standard, the CPIP certification program can unlock greater career opportunities for professionals and provide companies a competitive advantage, especially during challenging economic times. Learn more about the program at www.ISPE-PCC.org.

2009 CPIP Certification Program Examination Dates
9 March – 17 April, and 7 September – 16 October

ENGINEERING PHARMACEUTICAL INNOVATION ISPE

For more information on this or other ISPE technical documents and publications, visit www.ISPE.org/publications today!

This article is being reprinted with permission from the October 2008 issue of Regulatory Focus, the monthly publication of the Regulatory Affairs Professional Society (RAPS).

For more information about RAPS and *Focus*, visit www.raps.org.

Considering Outsourcing? Risks and Benefits for FDA-Regulated Firms

by Mukesh Kumar, PhD, RAC

From its modest start about 30 years ago as an alternative to academic institutions for laboratory and clinical work, outsourcing has grown into a $16 billion industry in the US alone. It spans all aspects of drug development, from discovery to clinical development to product approval, and even included commercialization and postmarketing support. With more than 90% of the biopharmaceutical industry comprised of small businesses with limited resources,[1] many firms outsource product development to either reduce expenses or compensate for lack of core competencies. Contract Research Organizations (CROs) offer an excellent outsourced resource to guide firms through the risky, costly, and time-consuming myriad of drug development pathways.

The cost of drug development has risen steadily over the last two decades, partly as the result of increased operational expenses, but mostly due to the need for increased knowledge of complex biological processes and the capability to monitor and understand safety-related aspects of drugs. The last decade also has seen high-profile cases where approved drugs were withdrawn due to unexpected safety issues not identified during development phases and promising therapies that failed at late stages of development. These have led the US Food and Drug Administration (FDA) to require increasing amounts of data to support new drug applications. Coupled with the drying up of product pipelines and loss of revenue due to several blockbuster drugs going off patent within a short span of time, this FDA requirement has exacerbated financial and operational problems for biopharmaceutical companies, both large and small. Changing industry dynamics have led to extensive, across-the-board cost-cutting measures.

But companies must innovate to survive. While they are striving to control costs, they also need to increase spending on R&D to create profitable new proprietary products. CROs offer a solution to this dilemma: they can develop drugs faster than pharmaceutical companies with comparable quality and lower overall cost. Large companies such as GlaxoSmithKline, Pfizer, and Wyeth have unveiled strategic shifts in new product development policies, relying increasingly on CROs for R&D and subsequent development.[2,3]

CROs are uniquely capable of addressing these issues because of their diverse product experiences (even within the same indications), infrastructural capabilities and high concentration of human resources. Approximately 500 CROs compete around the world.[4] Large CROs offer a wider range of services while smaller ones specialize in specific areas, from strategic consultancy to clinical or preclinical services. While large pharmaceutical companies still account for about 70% of the total revenue for the outsourcing industry, the share of the smaller companies is steadily increasing and is expected to continue growing over the next few years. Also, due to the globalization of drug development, there is a trend toward increasing revenue from outside the US. Currently, about 40% of CROs' revenues are generated outside the US and that figure is expected to rise to more than 60% by 2010. The CRO industry is growing at an annual rate of 12.6% and is expected to reach about $30 billion by 2011, with one of the highest earning rates per employee in any industry.[4]

Almost all biopharmaceutical companies need to consider outsourcing all or parts of their operations to CROs. The CRO industry has evolved from the tactical or transactional outsourcing model to the role of a strategic partner. And as in any partnership, the biopharmaceutical company needs to consider

several factors before deciding which CRO to work with. Among these are potential supply chains and markets, the risks and benefits of outsourcing operations to particular contractors (whether down the street or overseas), alternatives to outsourcing, and how to maintain an effective relationship with contractors and suppliers in producing safe, effective and compliant products for the marketplace. The main issues companies should consider before outsourcing are discussed below.

Harnessing Technology Assets: Building Core Competencies

CROs offer ready availability of core competencies that may be hard for the biopharmaceutical company to develop internally in a cost- and time-effective manner, but outsourcing could be considered as stunting the development of internal capabilities for conducting strategically important research at a later time. This is of particular concern for small and medium-size enterprises that look at working with more-experienced and technically advanced CROs as a means of training their personnel for future projects. Companies need to identify potential areas for building internal core competencies early on. Most small and medium-sized biopharmaceutical companies focus their core efforts on discovery, strategic planning and conducting smaller clinical trials locally; however, certain areas – such as animal testing and conducting research in countries where the biopharmaceutical company has little or no native expertise – are better left to the CROs. By targeting the areas for building core competency, a biopharmaceutical company can collaborate with the CRO to train its people on the job. This hands-on training must be complemented by training and education programs available in the public domain because interaction with the CRO cannot replace education.

Long-Term Interests

Companies with one or a few products rely heavily upon positive relationships with a few opinion leaders. These could be the individuals who discover the technology they are developing, or key investigators and consultants. Hence, developing long-term relationships with these individuals and organizations is critical for the company's survival. CROs might not be aware of the strategic importance of a particular investigator or site to the company. Since the CRO's job is to assure timely and high-quality project execution, they might get into a negative relationship with the key investigator on compliance-related issues. To avoid that, the CRO must be made aware of the logistical role of key investigators. Training and mentoring programs for key investigators can be built into the project to ensure higher compliance. This is particularly important for global trials where each country in which trial sites are located might have local high-profile investigators who are critical to the current project's completion and future company plans.

Concludes on page 70.

"Outsourcing is commonly misunderstood as unidirectional flow of contract work from the developed countries to emerging regions in Asia and Latin America."

Risk Mitigation

A key component of the decision to outsource usually is the desire to reduce the risk of failure in developing desired products. Companies seek strategic advice from the CRO about the best regulatory pathways, preclinical and clinical studies, safety monitoring and marketing research. A good consultant can help a company avoid costly mistakes, identify issues before they become concerns, and help develop contingency plans in case things do not happen as predicted. Companies tend to hire strategic consultants with whom senior managers feel comfortable sharing confidential information. Additional factors to consider are the CRO's operational experience: specifically, depth and width of expertise, technological advancement and global reach.

Strategic Partnership

The outsourcing industry has a come a long way from being used primarily for transactional or tactical services for specific tasks in the 1980s and 1990s, to serving as strategic partners participating in all aspects of drug development. As a result of their increased experience and technical capabilities, most CROs feel comfortable sharing development risks with their clients by working for equity or using deferred compensation models. CROs have developed highly skilled global teams that provide valuable global reach, not only for development steps but also access to new markets.

Discovery, which traditionally resided with the innovator company, is the latest activity to be added to the list of outsourced functions. The top biopharmaceutical companies lead in this new strategic shift in policy, where dedicated facilities are created by partners catering to the new molecule discovery needs of the client firm.

Most of the world's top pharmaceutical corporations have started reducing their in-house R&D budgets and increasing outsourcing to new regions of the world such as Asia – primarily India, China, and Singapore – and Latin America.[3] Small biopharmaceutical companies, similarly, can tap into this resource by outsourcing early-stage development steps to CRO partners, while concentrating their limited resources on high-end product management. There is a trend toward companies concentrating on senior management while outsourcing practically the entire development process to CROs. Of course, such extensive outsourcing poses an increased risk to small companies because of intellectual property concerns for mutually developed technologies, particularly when combined with strategic partnership agreements and equity or deferred compensation contracts. Such partnerships need extensive trust-building efforts and good legal contracts.

Conclusion

Outsourcing is commonly misunderstood as unidirectional flow of contract work from the developed countries to emerging regions in Asia and Latin America. However, the bulk of pharmaceutical contract research is done by CROs headquartered in the US and Europe. Rising operating costs worldwide, particularly in China and India, have led some analysts to predict a slowing of outsourcing to these areas, and even reversal of activities to the West. For biopharmaceutical firms, the need for strategic outsourcing and international localization of development steps cannot be emphasized enough. The place to start in developing an overall outsourcing strategy is with an honest appraisal of the contribution of all parties, including developers and the CROs, to the drug development value chain. The four keys to an effective outsourcing strategy are:

- identifying the appropriate tasks to outsource
- developing a rationale and process for CRO selection
- committing to managing CROs
- periodically reviewing deliverables

It is well accepted that outsourcing offers key advantages to biopharmaceutical companies of all sizes. However, for small and medium-size business, it could define the difference between being profitable and going out of business.

References

1. "FDA Final Rule Human Subject Protection." *Federal Register* Vol. 73, No. 82, 28 April 2008.
2. www.in-pharmatechnologist.com/Industry-Drivers/GSK-continues-shift-in-strategic-direction.
3. www.outsourcing-pharma.com/Preclinical-Research/GVK-BIO-secures-Wyeth-deal.
4. Hoang, T., et al. "Contract Research Helps Keep Drug Pipelines Flowing Sector Focus Report," Turner Capital Investment, Berwyn, Pennsylvania, July 2008. www.turnerinvestments.com/index.cfm/fuseaction/commentary.detail/ID/2661/CSID/387/.

About the Author

Mukesh Kumar, PhD, RAC is a senior director, regulatory affairs, at Amarex Clinical Research LLC, located in Germantown, Maryland, which is a full-service CRO offering strategic planning, trial management, data management, and statistical analysis services for global clinical trials. Kumar is a member of the Regulatory Affairs Professionals Society's Board of Editors for *Regulatory Focus*. He can be reached by email: mukeshk@amarexcro.com.

ESSENTIAL TO LIFE.

MARCH 17-19, 2009 • JACOB K. JAVITS CONVENTION CENTER • NEW YORK, NY

The Life Sciences industry is changing at a rapid pace. Advancements in technology, biologics, and medical devices continue to redefine the parameters of our industry.

To succeed in this ever-changing, ever-expanding global marketplace, it's absolutely essential to keep up with the latest developments, interact with your peers, and learn from industry thought-leaders.

For 30 years, INTERPHEX has been a beacon for the industry, the platform from which the industry grows and builds and where new innovations are introduced.

This year INTERPHEX is back in New York and co-locating with BIOTECHNICA America. And, like our industry, it has evolved to embrace all the latest advancements in Life Sciences manufacturing – from pharmaceuticals to biologics to medical devices to new technologies.

With the continued expansion and globalization of our industry, INTERPHEX is more essential than ever to your success. Be a part of this year's industry gathering in New York.

Register now to be a part of INTERPHEX*2009*. Visit www.interphex.com for FREE show admission, or call 1.888.334.8704.

Conference & Exhibition

INTERPHEX™

USA

- PHARMACEUTICAL
- BIOTECHNOLOGY
- MEDICAL DEVICES

CHINA 11, 2008 | PUERTO RICO 01, 2009 | MEXICO 04, 2009 | ASIA 06, 2009 | JAPAN 07, 2009 | **USA 03, 2009** | CANADA 09, 2009 | INDIA 09, 2009 | UK 05, 2010





Now's the time to register for INTERPHEX! Visit www.interphex.com now for FREE show admission. Questions? Call 1.888.334.8704.

Sponsored by: ISPE

Media Sponsors: PHARMACEUTICAL ENGINEERING. | Pharmaceutical processing | Pharmaceutical Technology

Featuring co-location with: BIOTECHNICA AMERICA

Media Supporter: PHARMACEUTICAL ENGINEERING.

Produced and managed by: Reed Life Sciences

Source Code: AD22

ISPE Starts Science and Technology Initiative in 2009

Project Encourages Greater Emphasis on Science and Technology to Advance Industry's Manufacturing and Distribution Performance

by Charles Hoiberg, Chairman of the ISPE International Board of Directors

Our global, not-for-profit Society that we have come to love during its 28 years of existence has grown close to 25,000 members in more than 90 countries and whose members are employed in industry, academia, and government as engineers, scientists, suppliers, and as regulators. So, for a simple chemist like me, this will be a complex operation to help manage. But, ISPE has gained prestige globally, in large part, because it has so many dedicated, talented, and engaged Members like you.

However, there are many significant challenges that will test the Society and our Members in the year ahead. One only needs to look at current stock prices for many of the leading firms, or the list of innovator drug products coming off patent, or the decreasing number of new drugs in the development pipeline to understand some of the pressures the industry is facing. This is in addition to the overall state of the global economy. Most firms are thoroughly examining how to reduce overhead and how to cut drug development and manufacturing costs. These troubling trends will undoubtedly have an impact on ISPE.

Another challenge is that as firms relocate more of their drug development and manufacturing sites to the Asia-Pacific region, ISPE Members' needs will change. We must react to this and design our offerings accordingly.

It is also evident that some traditional new chemical entity firms are realigning or expanding their business interests into the generic and the biotechnology areas. ISPE is not as well known in these sectors, but our tools and services are equally valuable to professionals in these fields. The Society must expand its reach into these areas.

Many large firms are also outsourcing more and incorporating many other parties, vendors, and suppliers into their business plans. ISPE needs to better connect with these professionals and more fully engage them.

We must ensure that ISPE is the professional development organization of choice. In other words, we must excel at being the best in serving our Members.

I strongly believe that ISPE can be a major resource to the industry and its regulators in these challenging times. Let me give you an important example. The approaches that many pharmaceutical firms are taking to develop and manufacture drugs are changing, in part due to the recent ICH Quality Guidelines Q8, Q9, and Q10.

It is assumed that as the business case for Quality by Design (QbD) is better appreciated, QbD will be increasingly implemented and the goal of achieving the "desired state" will be obtainable. The implementation of QbD also will impact and result in dramatic changes in the ways regulatory assessments and inspections may be performed.

Based on these realities, ISPE leaders held a strategic discussion during our annual planning retreat in July to develop a "Science and Technology" initiative to meet these needs. The vision is that ISPE will act as an integrator for all pharmaceutical disciplines to assist industry and regulators in advancing manufacturing science in order to achieve excellence in developing drugs and in pharmaceutical production.

We have defined Science and Technology as the collective term for the umbrella project that integrates the Society's understanding and advancement of manufacturing sciences. Manufacturing sciences is defined by ISPE as the integrated application of scientific knowledge, technical innovation, and

Concludes on page 75.

Global Suppliers Directory and More Available on INTERPHEX365 Web Site

Sponsored by ISPE, INTERPHEX365 (www.interphex365.com) provides a global online community where life science professionals can search an online global directory of industry suppliers, source active projects, and communicate directly with suppliers.

Users can connect with other professionals and find solutions to problems through online community networking, industry education, white papers, and Web seminars, as well as get the latest industry and regulatory news. Content from the pharmaceutical and life science industries is free with registration and is easily searchable and readily accessible year-round.

High-impact, low-cost advertising opportunities are available on INTERPHEX365. For more information, contact Dave Hall, ISPE Director of International Sales by tel: + 1-813-960-2105 Ext. 208 or email: dhall@ispe.org.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

ISPE-CCPIE Conference in China a Success

A very successful ISPE Conference was held in Beijing 11 to 12 November in cooperation with the China Center of Pharmaceutical International Exchange (CCPIE), an affiliate of the State Food and Drug Administration (SFDA).

The Conference was oversold with more than 260 delegates and many registrations had to be rejected due to venue capacity. The smooth delivery of the Conference resulted in positive feedback from delegates as they enjoyed one day of plenary sessions and a keynote address; one day for three parallel sessions on biotechnology, GAMP 5, and validation; and an elegant dinner reception for professional networking.

In addition, there were more than 20 renowned international speakers who delivered presentations. Keynote speakers included Bob Best, ISPE President and CEO; Mr. Bian Zhenjia, Director of Drug Safety and Inspection Department of the SFDA; Steven Wolfgang, Compliance Officer of the US FDA; Bob Tribe, ISPE Asia-Pacific Regulatory Affairs Adviser and Former PIC/S Chairman, and other high level officials from the SFDA, etc.

The Conference was held in conjunction with the 13th China International Pharmaceutical Industry Exhibition (China Pharm) which took place from 12 to 14 November 2008 at the China International Exhibition Centre. Sponsors of the event included DoveBid, Hewlett-Packard, NNE Pharmaplan, Pall Life Sciences, Pharm-Tech Magazine, Rockwell, and Shimadzu.

Bob Best, ISPE President and CEO at the ISPE-CCPIE China Conference.

In addition to ISPE's annual conference in China, CCPIE will cooperate closely with ISPE in a variety of ways, including providing training opportunities for the region. Visit www.ispe.org.cn for more information about conferences, training, and symposiums being offered in China.

Philippines Affiliate Launched

The challenges posed by the soon-to-be implemented ASEAN harmonized registration system for pharmaceuticals as well as dynamic regulatory requirements were some of the factors that prompted industry executives to form the ISPE Philippines Affiliate.

With more than 90 participants from various pharmaceutical companies and academe, the Philippines Affiliate was launched at the Wyeth Training Centre in Makati on 10 October 2008.

Talks about forming the Affiliate started in February 2008 with eight volunteers who saw the value and benefits of ISPE in the country. After eight months of preliminary work, the Affiliate was finally launched in the Philippines.

The board consists of 15 volunteers, all of whom are professionals in the industry and academe. The Affiliate will work in conjunction with ISPE to extend benefits to local members and to promote networking and interaction between professionals within the pharmaceutical industry. The Affiliate also aims to deliver a program throughout the year that is beneficial to members and will address the current concerns/issues within the industry. The Board hopes that the presence of ISPE in the Philippines can help promote and develop a pharmaceutical and engineering infrastructure in the country.

Klara Tisocki, Drug Registration Specialist currently with BFAD as a consultant, and Peter Tan, ISPE Asia Pacific Affiliate Relations Manager, were guests at the launch. Tan gave a brief introduction on the benefits of ISPE membership to the attendees present. The attendees also were encouraged to sign up as volunteers for the different committees within the Affiliate.

Participants from 30 Countries Attend Successful PIC/S-PDA-ISPE Workshop in Geneva

In conjunction with the Committee meeting, PIC/S in partnership with ISPE and the Parenteral Drug Association (PDA) organized an interactive joint workshop on the "Manufacture of Sterile Medicinal Products (EU-PIC/S GMP revised Annex 1)" in Geneva on 13 to 14 November. It was the second time that PIC/S co-organized such a joint event with professional and industry associations.

The meeting was open to both regulators and industry. It was attended by more than 80 participants (among which 50% came from Regulatory Authorities) representing around 30 countries.

The workshop started with a plenary session, including presentations on the interpretation of the revised Annex 1 and on inspection experiences from both regulators' and industry's perspectives. GMP inspectors and industry representatives also participated in practical workshops (case studies) on the capping of vials, media fills (process simulations), the continuous monitoring, the clean area classification and ISO norms, as well as on the sterilization and depyrogenation of contact parts and containers.

The workshop was unanimously considered as a success by both inspectors and industry representatives. More joint workshops will likely be organized with these professional and industry associations in the future.

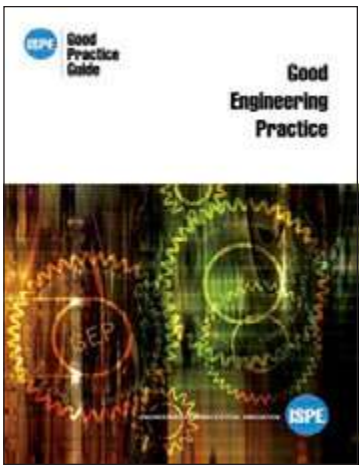
Guide on Good Engineering Practice Released

In November 2008, ISPE released the first edition of the ISPE Good Practice Guide: Good Engineering Practice.

"Good Engineering Practice (GEP) is defined as the minimum engineering methods and standards that are applied throughout the lifecycle of an asset to deliver fit for purpose and cost effective solutions," said Chris Derrett, Chair of the ISPE Good Practice Guide: Good Engineering Practice Task Team.

This Guide covers the complete lifecycle of engineering from concept to retirement. The Guide:

- aims to promote a common understanding of a benchmark definition that could be usefully employed in assessing an individual company's practices
- is aligned with the pharmaceutical industry, recognizing that the GEP core concepts that apply universally through specific practices vary from industry to industry
- identifies key attributes of GEP, including how GEP relates and interfaces with GxP



For additional information and the complete table of contents, please visit www.ISPE.org/publications.

Project Encourages Greater Emphasis on Science and Technology...

Continued from page 72.

quality risk management to deliver product and process understanding.

Product Quality Lifecycle Implementation (PQLI) is an initiative focused on providing guidance on best practice implementation of the concepts described in ICH Guidelines, particularly Q8, Q9, Q10, and the future Q11.

Starting in 2009, Science and Technology will be a system set up within ISPE to work with industry and regulatory leaders worldwide to encourage a greater emphasis on science and technology to advance and enhance the manufacturing and distribution performance of the pharmaceutical industry.

It will generate a Science and Technology pipeline of projects for ISPE to develop, advance, and disseminate to its Members. The initial emphasis will be to promote PQLI and the further development of pragmatic and practical implementation of ICH and related guidelines — such as Q8, Q9, Q10, and Q11 — based on sound scientific, engineering, and business principles.

What has been completed to date are five published papers in the June issue of ISPE's *Journal of Pharmaceutical Innovation* (JPI). What is currently in progress is a case study document led by the Control Strategy group. What our future plans involve are an integration paper, case studies, additional JPI articles, and technical guidance documents.

As implied by the project name, PQLI encompasses the total lifecycle of a pharmaceutical product from development through regulatory approval into commercial manufacturing and finally termination. It also encompasses all manufacturing and production activities, including raw materials, APIs and drug product production, facilities design and operation, and product distribution.

The Society will develop a multi-horizon plan for the Science and Technology initiative through PQLI that ensures a continuous flow of the best of science and technology to all sectors of membership. We think the Science and Technology and PQLI initiatives are good examples of the way ISPE can play an important role in helping the industry and regulatory authorities find practical solutions to move into the future.

Yes, the challenges ahead of us are many, but I am very optimistic that ISPE is adapting its programs and business plans so it will remain a leader, a catalyst of change, an innovator, and a valuable resource to all.

As the ISPE Chairman of the International Board for the next 12 months, I sincerely thank you — the ISPE Members — for the privilege of serving you.

Architects, Engineers – Constructors

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

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

Architects, Engineers – Constructors (cont).

Parsons, 150 Federal St., Boston, MA 02110. (617)-946-9400. See our ad in this issue.

Aseptic Filling

Aseptic Technologies, Rue Camille Hubert 7-9, 5032 Les Isnes, Belgium. +32 81409410. See our ad in this issue.

Cleanroom Products/Services

AES Clean Technology, 422 Stump Rd., Montgomeryville, PA 18936. (215) 393-6810. See our ad in this issue.

Plascore, 615 N. Fairview, Zeeland, MI 49464. (800) 630-9257. See our ad in this issue.

Consultants

Employment Search Firms

Jim Crumpley & Associates, 1200 E. Woodhurst Dr., Bldg. B-400, Springfield, MO 65804. (417) 882-7555. See our ad in this issue.

Filtration Products

MKS Instruments, 5330 Sterling Dr., Boulder, CO 80301. (800) 345-1967. See our ad in this issue.

Siemens Water Technologies, 10 Technology Dr., Lowell, MA 01851. (978) 934-9349. See our ad in this issue.

Homogenizers

GEA Niro Pharma Systems, 9165 Rumsey Rd., Columbia, MD 21045. See our ad in this issue.

Instrumentation

Hach Ultra Analytics, 5600 Lindbergh Dr., Loveland, CO 80539. (970) 663-1377. See our ad in this issue.

Passivation and Contract Cleaning Services

Active Chemical Corp., 4520 Old Lincoln Hwy., Oakford, PA 19053. (215) 676-1111. See our ad in this issue.

Cal-Chem Corp., 2102 Merced Ave., South El Monte, CA 91733. (800) 444-6786. See our ad in this issue.

Concludes on page 78.

Rupture Discs

Fike Corp., 704 SW 10th St., Blue Springs, MO 64015. (816) 655-4546. See our ad in this issue.

Sterile Products Manufacturing

Tanks/Vessels

Lee Industries, PO Box 688, Philipsburg, PA 16866. (814) 342-0470. See our ad in this issue.

Used Machinery

Validation Services

Commissioning Agents, Inc., 1515 N. Girls School Rd., Indianapolis, IN 46214. (317) 710-1530. See our ad in this issue.

Valves

Gemu GmbH & Co., Fritz-Mueller-Str. 6-8, D-74653 Ingelfingen, Germany. +49 7940123-0. See our ad in this issue.

Gemu Valves, 3800 Camp Creek Pkwy., Bldg. 2600, Suite 120, Atlanta, GA 30331. (678) 553-3440. See our ad in this issue.

Vial Traying Systems

Hurst Corp., Box 737, Devon, PA 19333. (610) 687-2404. See our ad in this issue.

Water Treatment

Elettracqua Srl, Via Adamoli 513, 16141 Genova, Italy. +39 0108300014. See our ad in this issu.

Siemens Water Technologies, 10 Technology Dr., Lowell, MA 01851. (978) 934-9349. See our ad in this issue.

ABB **25**
ACTIVE CHEMICAL **79**
AES CLEAN TECHNOLOGY **27**
ASEPTIC TECHNOLOGIES 31
CAL-CHEM CORP. **53**
COMMISSIONING AGENTS **37**
CRB CONSULTING ENGINEERS **3**
JIM CRUMPLEY & ASSOCIATES **78**
EI ASSOCIATES 65
ELETTRACQUA **43**
EMERSON PROCESS MANAGEMENT **51**
ENVIRONMENTAL TECTONICS CORP. 59
FARR AIR POLLUTION CONTROL **2**
FIKE CORP. **49**
GE WATER & PROCESS TECHNOLOGIES 61
GEA PROCESS ENGINEERING **11**
GEMU GMBH **75**
GEMU VALVES **63**
HACH COMPANY **19**
HURST CORP. **78**
IMA ACTIVE **69**
IMA EDWARDS **15**
INTELLIGEN **13**
INTERPHEX **71**
KINETICS **57**
LEE INDUSTRIES **17**
MKS INSTRUMENTS **23**
NNE PHARMAPLAN **80**
OPTIMA MACHINERY **76**
PLASCORE **33**
PARSONS **5**
PHARMACEUTICAL ONLINE 77
PROSCON 73
SIEMENS WATER TECHNOLOGIES **29**
TELSTAR 9
VALIDATION TECHNOLOGIES 39
WESTFALIA SEPARATOR 45
WILDEN PUMP & ENGINEERING 47

more
than engineering

We are determined to support and **improve technologies** and **standards** in the pharma and biotech industries.

Winner of the ISPE award 2008
Company of the Year

Consulting | Engineering | Construction | Validation | Solutions

NNE Pharmaplan is one of the world's leading engineering and consulting companies. We enable pharma and biotech companies to bring products to market with fast, innovative and reliable services.
We employ more than 1500 people at over 20 locations worldwide.

nne pharmaplan®

nnepharmaplan.com