Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
November/December 2008, Vol. 28 No. 6

Evaluation of Electron Beam (E-Beam) Sterilization Technology for Filling of Drug Products in Pre-Filled Syringes (PFS)

This article presents a science-based strategy to evaluate the suitability of Electron Beam (E-Beam) sterilization technology for the filling of protein-based products in Pre-Filled Syringes (PFS).

by Xiaogang Pan*, Xiangning Deng*, Michael Lee, Thomas O'Sullivan, Edwin Torres, Adrian Distler, and Narinder Singh

*These authors contributed equally to this article.

Introduction

Over the last decade, pre-sterilized and pre-washed syringes with closures have gained in popularity over traditional bulk syringes in the biopharmaceutical industry, owing primarily to increased operational efficiency through eliminating the requirements for syringe barrel washing, siliconization, and sterilization prior to filling process. Pre-sterilized syringes are packaged in sterile, pre-nested tubs, sealed with a cover, and individually bagged. However, challenges remain in the handling of these tubs when using high speed filling lines in barrier isolator systems. The sealed, pre-sterilized, individual tubs must be removed from their protective outer bags, and the tub surface must be sterilized prior to their transfer into a barrier isolator filling system. The selected sterilization process should best fit the product and production process requirement, achieve the desired Sterility Assurance Level (SAL), and not create byproducts or degrade closures, which may have an impact on biopharmaceutical products. Successful surface sterilization processes should ensure the quality of pharmaceutical primary packaging components with minimal regulatory, environmental, product, or facility impact concerns as well as enhancing patient safety and operational effectiveness.

Common Technologies for Packaging Surface Sterilization

The most common methods available to clean the surfaces of pre-sealed packaging include chemical processes, such as the application of Isopropyl Alcohol (IPA) or Ethylene Oxide (EtO) gas; and physical processes, such as stream, dry heat, and irradiation from UV, gamma ray, or Electron-Beam (E-Beam). Each of these technologies is different and has inherent aspects that could make it either suitable or undesirable for a particular sterilization process.

As chemical agents, IPA sanitization and EtO sterilization are effective in microbial load reduction. Nevertheless, IPA is not effective to spores of bacteria, and EtO could leave potentially hazardous residuals on the surface of the packaging materials or pre-sterilized components through penetrating the sterile envelope. Both of these technologies will require controlled parameters for contact and exposure to be effective and will require additional aeration processes in order to dispel residues before further handling.[1,2]

UV irradiation to inactivate microorganism is well understood, efficient, and cost effective.[3,4] UV sterilization depends on direct line-of-sight optical exposure to the surface of material to be sterilized. Hence, any cavities or unexposed areas that could likely hide microorganisms from UV exposure may be a real concern. UV irradiation has low penetration relative to the other higher power irradiation processes and is suitable for surface sterilization; however, it may not be suitable for other deep penetration application. The UV light source has a relatively short life span compared to the Gamma or E-beam sources. Therefore, although a UV sterilization system is low cost to install, non-capital associated cost could be higher based

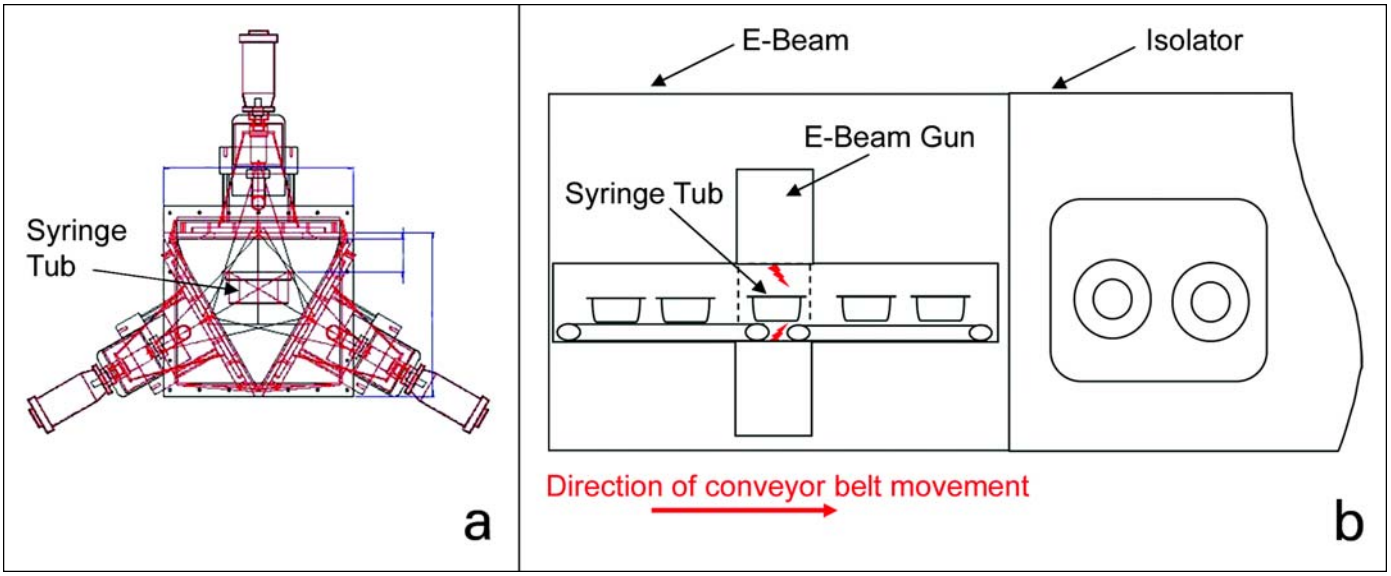


Figure 1. Schematic drawing of an E-Beam System: a) Cross-section view of the three electron emitters (guns) (Courtesy of LINAC Technologies, Orsay, France), b) Illustration of integrated E-Beam and Isolator system.

on continuous monitoring and calibration.

Gamma irradiation, a form of high energy photon commonly generated from an irradiator containing an isotope, such as Cobalt-60, possesses excellent penetrative capability and leaves no residuals on either the package surfaces or within the nested tub. However, deep penetration may cause certain packaging materials to be structurally altered or even degrade, which can be seen in syringe barrel discoloration.[1,5] In addition, the gamma irradiation contractor may have to purge the irradiator between batches that use different doses.[6] That means reduced throughput of the whole operation process. Gamma irradiation has been used in industry to pre-sterilize syringe tubs, but not immediately before product fill. Additional exposure to the exterior of the tubs immediately before use will require the end user to conduct extensive studies on compound effects.

E-Beam applies a concentrated, highly-charged stream of electrons[7,8,9] to perform surface sterilization. E-Beam technology has a lower irradiation penetration and a short exposure time than Gamma irradiation process for surface bioload reduction. Unlike Gamma irradiation, E-Beam sterilization is capable of being switched on or off at will, and potentially offers high throughput capability.

E-Beam Technology for Sterilization of Syringe Tub Surface

E-Beam sterilization could replace the manual IPA application and surface wipe used on the pre-sterilized syringe tub surfaces. It can be used in conjunction with the barrier isolation technology or classic cleanroom applications supporting high-speed aseptic filling processes. This technology would provide greater assurance of surface sterilization supporting the sterility of the sealed syringe tubs. Other advantages include reduction in the number of operators needed in materials handling and manual interventions, sterilization without chemical disinfectant, and providing a more compliance-oriented system and validatable reproducible process that is designed for integration with high-speed filling lines.

In a typical E-Beam system, debagged syringe tubs are loaded into the system via an infeed "mousehole," and carried by conveyor through the system tunnel across the high energy electron beam curtain and into the filling isolator. The high energy electron beams are produced by three electron emitters triangularly positioned around a single moving tub on the conveyor belt - *Figure 1*. The design intends to ensure a complete coverage of electron beam on the exterior surface of syringe tubs with the goal to achieve adequate sterility assurance, usually a 6-Log reduction of appropriate challenge microorganism, such as Bacillus Pumilus.

Although E-Beam technology has been successfully employed in sterilizing food, medical devices, and diagnostic products since the late 1980s, it is still mostly considered as an alternative technology within the pharmaceutical and biotechnology industries.[10] As of 2006, approximately a dozen E-Beam systems were operating in the global pharmaceutical industry. A key concern of E-Beam technology for oxidation-sensitive protein drug product application is that the high-energy electrons ionize oxygen in air and generate Ozone. The Ozone, which is generated inside the tub or permeated into the tub, would pose a challenge for potential biopharmaceutical end users. In addition to the potential oxidation effect of residual Ozone on drug products (protein molecules) in the syringes, Ozone oxidation also may lead to changes in the syringe component surface chemistry and/or leachable/extractable levels, which may subsequently affect the stability of protein based drug products.

$$O_2 + e^- (high \bullet energy) \rightarrow 2O^\bullet + e^- (low \bullet energy)$$
$$O^\bullet + O_2 \rightarrow O_3$$

Implementing the new E-Beam sterilization technology into biopharmaceutical manufacturing processes requires exten-

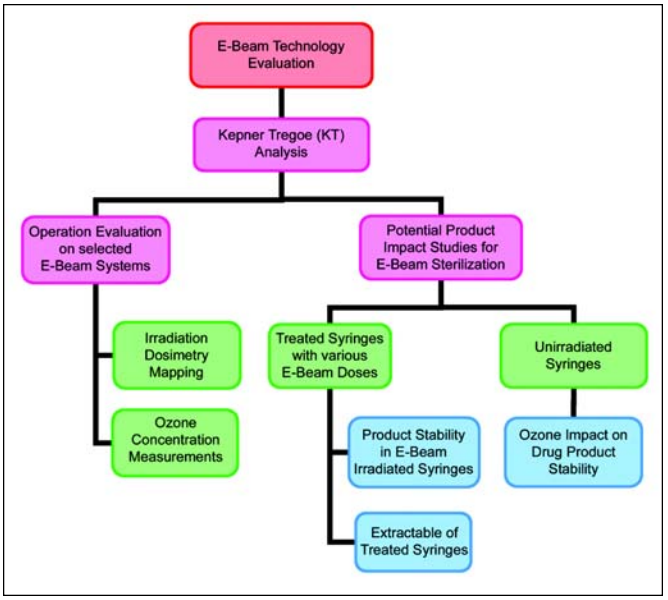


Figure 2. Strategy for evaluation of E-Beam technology.

sive information evaluation, decision integration, process understanding, and product development. This article presents a science-based strategy to evaluate the suitability of E-Beam sterilization technology for the filling of protein based products in Pre-Filled Syringes (PFS).

Overview of E-Beam Sterilization Technology Evaluation Strategy

To better understand E-Beam sterilization technology and its potential impact on final drug products, an evaluation strategy was applied. This strategy consisted of three aspects - *Figure 2*:

1. Kepner Tregoe (KT) analysis to evaluate selected key criteria on five possible E-Beam designs from different vendors
2. *in situ* E-Beam machine operational evaluation at the vendor location with irradiation dosimetry mapping and Ozone concentration measurements in the selected E-Beam system
3. use of drug product impact studies to investigate the extractable profiles generated from E-Beam treated syringes components, stability testing of drug products filled into E-Beam treated syringes, and an evaluation of the stability of filled drug product interacting with different levels of Ozone residual entrained within the syringe headspace. Details of the evaluation strategies, studies, and testing are described below.

E-Beam Technology Evaluation by Kepner Tregoe (KT) Analysis

Kepner Tregoe (KT) is an analysis tool for ranking and weighing criteria considered critical for a decision and assessing the potential risk associated with that decision.[11] To select an E-Beam system that would be deemed to be most successful for manufacturing protein based drug products, five E-Beam designs from three major vendors were comprehensively evaluated following KT analysis. In the criteria relationship matrix - *Figure 3*, each criterion was assigned a weight (c_i) based on performance, operational impact, economic effect, and timeline urgency in order to prioritize the criteria. A rating (d_{ij}) also was given to each E-Beam design based on how well that design fit the selection criterion. The total score s_i of each design was defined from the weights c_i of the criteria and the calculated grades d_{ij}, as seen in the equation (1) below:

$$s_i = \sum_{i=1}^{n} c_i \cdot d_{ij} \qquad (1)$$

A cross functional team consisting of Process Development, Operations, Quality, and Regulatory appropriately weighted

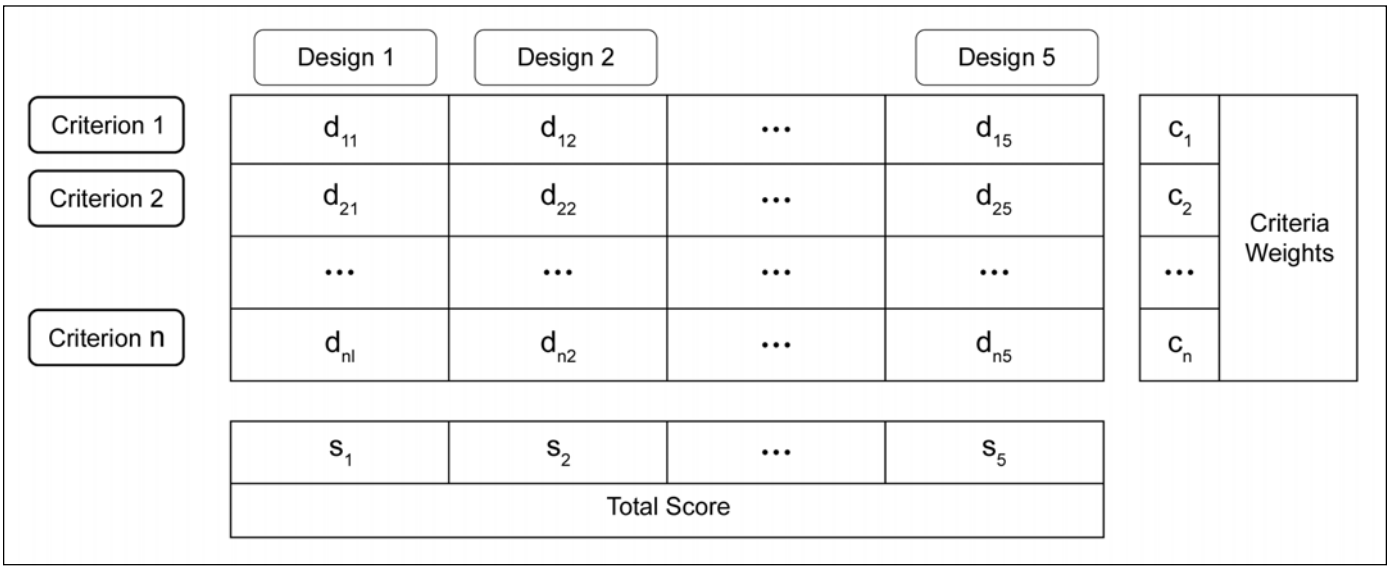


Figure 3. Criteria relationship matrix for KT analysis.

No.	Description	Rationale	Assigned Weight
1	Speed / Throughput	Filling line Capacity	5
2	Cleanability	Accessibility to E-Beam tunnel for cleaning purposes	7
3	Equipment Cost	Initial capital expenditure	5
4	In Process Dosage Measurement	Ability to monitor in-process dosage delivered to tubs	7
5	Dosage Adjustment Capability (Low and High)	Ability to adjust dosage delivered to the tub – ability to control penetration of electron beam	14
6	Conveyor Reversal Capability	Ability to run the conveyers in reverse mode to retrieve tubs without mechanical intervention	15
7	Proven Technology – Guns and Conveyers	Technology known to be in commercial use in pharmaceutical industry	19
8	Gun Replacement Time	Ability to reduce down time with gun changeover	6
9	Reliability (Arcing/Equipment Quality)	Equipment performance and projected usable life	14
10	Ozone Concentration inside Syringe Tub	Potential product impact	19
11	Tub Buffering Capacity	Ability to maintain working buffer of tubs to feed fill line in event of interruption to operations	8
12	Gun Technology	Type of technology used/dosage variability/startup time/window film/preventative maintenance/vacuum system used	12
13	Particle Generation	Particulate matter generated from the systems (conveyers, gun attractions, etc)	15
14	Tunnel Weight	Facility design impact	7
15	Service	Evaluation of vendor ability to provide adequate service preventing down-time	10

Table A. List of several criteria and assigned weight employed in the KT analysis.

these criteria. Table A provides a partial listing and description of several criteria employed in the E-Beam KT analysis.

Operational Evaluation of Selected E-Beam System

The projected robustness and efficacy of the selected E-Beam system was subjected to further evaluation under conditions that simulated operational requirements. Dosimetry mapping, Ozone concentration testing, and system endurance testing were carried out at the vendor site. Dosimetry mapping was performed to confirm the applied irradiation doses used to surface decontaminate the sealed syringe tubs on the selected E-Beam machine. Ozone concentrations found below the sealed lid were measured inside the tubs for each applied irradiation dose immediately after the tub passing through the E-Beam machine. System endurance testing was performed to measure the process and throughput rates and identify potential operational issues. Syringe tubs obtained from three different vendors were subjected to E-Beam irradiation.

Irradiation Dosimetry Mapping

To verify the E-Beam machine set-up, four different irradiation doses (0, 25, 2 × 25, and 50 kGy [Gray]) were included in the dosimetry testing - *Table B*.[12] Selection of the irradiation scheme above was based on the normal operating parameters of the E-Beam system and projected operations use of the system. Specifically, the 0 kGy condition represented untreated control, and the 25 kGy condition was deemed to be the normal operational condition with minimally acceptable irradiation dose.[13,14] The 2 × 25 kGy condition was intended to simulate a possible scenario where the syringe tubs may have been treated by E-Beam, but were not used for product filling and had to be removed, possibly to clear a jam further downstream in the filling process. As such, they could potentially be exposed to E-Beam irradiation dosing twice prior to use. Alternatively, syringe tubs may be subjected to E-Beam irradiation twice during system re-start following a gun arcing event or other machine malfunctions. Finally, the 50 kGy condition was intended to provide a maximum design exposure limit to evaluate impact of dosing and to set a limit for the E-Beam operational parameters.

Irradiation Dose (kGy)	Treatment Process
0	Control. Passing through E-Beam with electron guns turned off.
25	Standard irradiation. Passing through E-Beam with electron guns turned on.
2 × 25	Passing through E-Beam twice consecutively with electron guns turned on.
50	Passing through E-Beam with electron guns turned on. Conveyor speed is one-half of that for the 25 kGy condition.

Table B. E-Beam irradiation dosage for syringe tubs treatment.

The E-Beam treatment process is intended to project sufficient irradiation (25 kGy) to only the exterior surfaces of the sealed, pre-sterilized syringe tub, and to penetrate through the first Tyvek® layer on top of the tub. However, the possibility cannot be ruled out that a small amount of irradiation (< 5 kGy) could reach the nested syringes located below the third Tyvek® layer (assuming a double-ply Tyvek® liner inside the tub). In order to assess the irradiation doses applied to different areas on and inside the syringe tub, 15 dosimeters (B3 WINdose Dosimeters, GEX Corp., Centennial, CO) were affixed to various positions of the syringe tub - *Figure 4*. After passing through the E-Beam machine, the exposed tub was incubated at 65°C for 30 minutes to stabilize the irradiation dosimeter for complete color development.[15] The dosimeters were then removed from the tub and measured for absorbance at 554 nm (A_{554nm}) using a spectrophotometer (Model GENESYS 20). The corresponding irradiation doses were obtained using a conversion chart provided by the dosimeter manufacturer. If an actual A_{554nm} dosimetry reading did not appear on the chart, the corresponding irradiation dose was then read from the closest lower value on the chart, ensuring that the actual irradiation dose received was no less than the vendor's claim.

Ozone Concentration Measurement

For each applied irradiation dose, Ozone residual concentrations inside the tub were measured by testing three syringe tubs on an Ozone Analyzer. These tubs were specially modified by the E-Beam system vendor for Ozone measurement. A hole was drilled through the tub sidewall and tubing was inserted into the tub to provide an air sampling point.

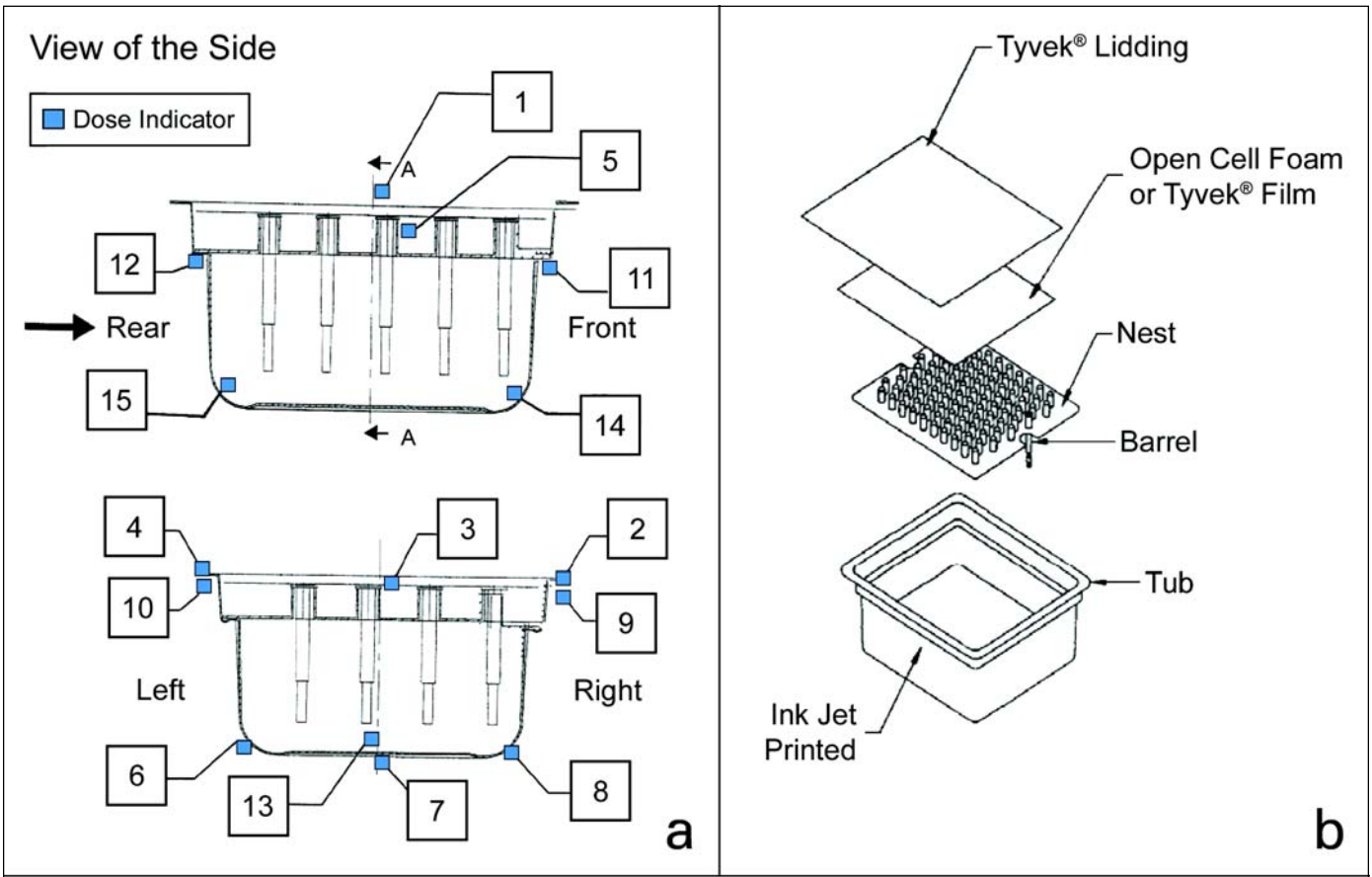
Immediately after passing the three tubs through the E-Beam machine, the Ozone concentrations inside each tub were sequentially measured at specified time intervals up to three minutes. Since Ozone inside the tub could freely permeate through the Tyvek® lid back into atmosphere, the highest reading for each tested tub was considered the actual Ozone residual concentration achieved.

Product Impact Studies

The strategy for evaluating the potential impact on drug product from E-Beam technologies was illustrated in Figure 2. Three studies were designed to assess the potential impact on product from E-Beam sterilization:

1. extraction studies for E-Beam irradiated syringe components
2. stability of protein drug products filled in E-Beam irradiated syringes
3. drug product quality impact testing from Ozone exposure

Syringes from three vendors were irradiated with four different irradiation doses (0, 25, 2 × 25, and 50 kGy). Extraction studies were performed on these treated syringes for extractable profiles by LC-MS/UV (Liquid Chromatography – Mass Spectrometry and GC-MS (Gas Chromatography – Mass Spectrometry). Four representative drug products were filled into the E-Beam treated syringes. These drug products were placed



#	Dosimeter Position	#	Dosimeter Position	#	Dosimeter Position
1	Top Center	6	Bottom Corner (Left)	11	Under Middle Second Step (Front Side)
2	Under the First Sheet of Tyvek® (Middle Right Edge)	7	Bottom Center	12	Under Middle Second Step (Back Side)
3	Under the First Sheet of Tyvek® (Center)	8	Bottom Corner (Right)	13	Bottom Center (In Tub)
4	Under the First Sheet of Tyvek® (Middle Left Edge)	9	Under Middle Right Edge	14	Inside Right Corner (In Tub)
5	Under the Third Sheet of Tyvek® (Center)	10	Under Middle Left Edge	15	Inside Left Corner (In Tub)

Figure 4. a) Positions of dosimeter placement around a syringe tub, b) Schematic diagram of the double-ply syringe tub. Note: Positions 14 and 15 were diagonally placed.

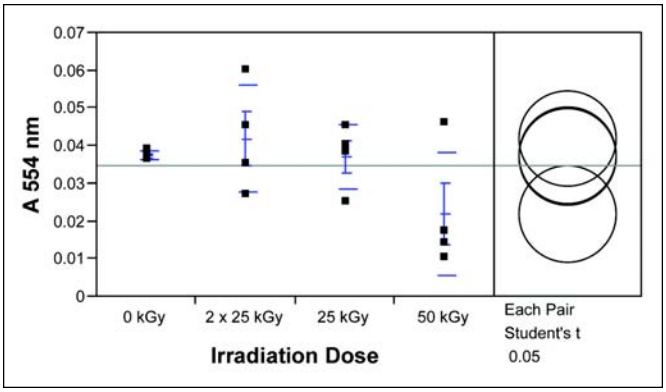


Figure 5. One-way analysis of A554 nm by irradiation dose. Note: Comparison of residual in-tub irradiation levels after E-Beam sterilization under various conditions. The in-tub irradiation levels are represented by $A_{554\ nm}$ readings at Positions 5, 13, 14, and 15 in Figure 3.

into their product specific stability programs and then evaluated at various time points using appropriate analytical methods.

The potential impact from Ozone was evaluated by introducing various concentrations of Ozone concentrations: (0, 0.2 - 0.5, 1.8 - 2.2, and 18.0 - 22.0 ppm) into the headspace of drug products Pre-Filled Syringes (PFS). These products were placed into their product specific stability programs and then evaluated at various time points using appropriate analytical methods, focusing on assessment of oxidation statuses and ensuing changes in protein conformation, degradation, and/or aggregation.

Statistical Analysis

The upper 99% confidence limit of the in-tub Ozone residual concentrations and their probability to exceed the vendor claimed maximally allowable Ozone concentration (0.2 ppm) was calculated, assuming normal distribution of the concentration values.

Results and Discussions

KT Analysis Summary

Based on the scores from the KT analysis, E-Beam Design 1 obtained the highest score among the five candidate designs. Several advantages of Design 1 included horizontally oriented conveyor systems, a fully integrated containment tunnel, gentle tub movement during transfers in the conveyer system's reverse mode, and more buffering capacity. Therefore, Design 1 was determined to have the greatest probability to be successfully integrated with a high-throughput (> 300 units/minute) syringe filling line. The robustness and efficacy of the recommended E-Beam design was subject to further operational evaluation.

E-Beam System Operation Evaluation Results

Dosimetry Mapping

Dosimetry mapping was carried out to confirm the irradiation doses applied to treat the syringe tubs on the recommended E-Beam machine design. Under the 0 kGy condition, all 15 dosimeters showed irradiation doses at less than 4 kGy (lowest data point on the conversion chart), indicating that inadequate irradiation was applied inside the tubs. Under the 25 kGy condition, all dosimeters located on the outer surface of the tub received irradiation doses equal to, or greater than, 25 kGy, the required sterilization dose to provide a 6 log reduction.[13,14] Under the 2 × 25 kGy and the 50 kGy conditions, all tub surface positions (Positions 1-4 and 6-12) received irradiation doses greater than 50 kGy. Therefore, the sterilization parameters (gun current, scan width, and belt speed) were capable of delivering acceptable irradiation doses to syringe tubs. It should be noted here that an irradiation dose of 13 kGy is sufficient for a 3 log reduction for surface decontamination purpose.[11] Nevertheless, 25 kGy was used as the minimally accepted irradiation dose for our evaluations.

All dosing positions measured under the third Tyvek® sheet (Tyvek® cover plus a double Tyvek® liner; referring to positions 5, 13, 14, and 15) received an irradiation dosing of less than 4 kGy under all conditions. No significant increases were observed for the corresponding A_{554nm} readings at these positions when the irradiation doses increased from 0 to 50 kGy, indicating that the syringes inside the tub were not radiation sterilized - *Figure 5*. The syringes within the tub under normal use conditions will be pre-sterilized, so limiting additional dosing is a key feature of this technology. The nominal irradiation dose may be increased in order to ensure that an irradiation dose of no less than 25 kGy is applied to the exterior tub surfaces without producing significantly more irradiation to the syringes nested within the sealed tub. In addition, the lower residual levels of irradiation (< 4 kGy) measured inside the tubs also provided the lowest levels of generated Ozone residual.

Ozone Concentration Measurement

Ozone concentration readings inside the syringe tubs remained lower than 0.2 ppm under all measured E-Beam irradiation conditions. The highest reading was obtained under the 50 kGy condition at 0.090 ppm. This value was greater than the maximal value obtained under the 2 × 25 kGy condition at 0.062 ppm, probably because the tubs were

Irradiation Dose	Highest Ozone Concentration Reading (ppm)			Mean	STDEV	Upper 99% CL (ppm)	Probability of > = 0.2 ppm
	Tub 1	Tub 2	Tub 3				
0 kGy	0.006	0.006	0.004	0.005	0.001	0.008	0
25 kGy	0.047	0.036	0.030	0.038	0.009	0.058	0
25 kGy × 2	0.062	0.057	0.041	0.053	0.011	0.079	0
50 kGy	0.090	0.081	0.044	0.072	0.024	0.128	7.044×10^{-8}

Table C. Confidence Limit (CL) estimation for Ozone concentration inside tub during E-Beam sterilization.

removed out of the E-Beam and re-processed under the latter condition, thus allowing more Ozone gas to be passing through the Tyvek® lid into the atmosphere before re-treatment and measurement. This rationale was supported by the fact that under each irradiation condition, the highest Ozone concentrations identified in Tub 2 and Tub 3 were found to be sequentially lower than the concentration measured in Tub 1.

Further statistical analysis - *Table C* using the highest Ozone concentration value from each of the three tested tubs showed that under all four irradiation conditions, the upper 99% Confidence Limits (CL) of the Ozone concentrations were still less than 0.2 ppm (the upper 99% CL of the tubs exposed under the 50 kGy condition was actually measured at 0.128 ppm and was worst case). Additionally, the probability of Ozone concentrations entrained within the tub, among the nested syringes, exceeding the upper specification limit of 0.2 ppm was close to zero (where $P = 7.044 \times 10^{-8}$ for expected Ozone in tubs treated under the 50 kGy dosing conditions). Therefore, the data supports the hypothesis that the nominal irradiation dose ($\geq$ 25 kGy) may be increased in order to ensure an applied surface irradiation dose of no less than 25 kGy will be measured on all of the tub's exterior surfaces without producing excessive Ozone inside the syringes nested within the sealed tubs.

Because the irradiation doses measured inside tubs (< 4 kGy) were much lower than those measured on tub surface ($\geq$ 80 kGy), the residual Ozone concentration detected inside tubs could have two possible origins: 1. it could have been generated in the E-Beam chamber and could then have permeated the tubs as it passed through Tyvek® sheets into the syringes; 2. it could have been generated inside tubs by residual electron irradiation created during E-Beam treatment.

The dosimetry mapping and Ozone concentration measurements confirmed that the Design 1 met the acceptance criteria as outlined in - *Table D*. This study showed that the E-Beam system tested was capable of delivering sufficient irradiation dosing (applying no less than 25 kGy) to all of the exterior tub surfaces. Additionally, even after two consecutive dosing treatments (2 × 25 kGy) or after exposure to a single double-dose treatment (an applied dose of 50 kGy), the irradiation levels inside the sealed tub remained less than 4 kGy and were comparable to the control group (0 kGy), while the Ozone concentrations inside the nested syringe headspaces inside the sealed tubs were significantly lower than 0.2 ppm.

Product Impact Studies

Extractable Profile Comparison of E-Beam Treated Syringes

E-Beam irradiation impact on the syringe extractable profile was evaluated. The extractable data from the syringe barrels was supplied by two vendors, had similar profiles, and the amount under all irradiation doses was measured and evaluated against the vendor standard. The data verified that E-Beam sterilization at an applied dose of 50 kGy dose did not impact the normal extractable profile of the syringes material of construction when compared to the profile results provided by these two vendors. However, syringes from the third component vendor were observed to have a slightly changed profile when exposed to higher irradiation doses (for application doses of both 2 × 25 kGy and 50 kGy), implying a likely quality impact to these syringes when subjected to repeated E-Beam processing or higher irradiation doses.

Product Impact from E-beam Treated Syringe

Four protein drug products were filled into the pre-irradiated syringes. Filling was followed by stability study under two different incubation conditions at 2 - 8°C (real-time) and 37°C (accelerated). The four drugs were selected to bracket the types of protein drug products.

This study was designed to address whether or not E-Beam irradiation could impact the syringe components, especially to the inner surface of syringe barrels, which could subsequently affect the stability of drug products filled into those syringes. A review of the six-month stability data, from

Irradiation Dose	Dosimetry Testing Acceptance Criteria	Ozone Testing Acceptance Criteria
0 kGy	• Maximum dose under the Tyvek cover at any point of the sheet (Positions 2, 3, and 4 in Figure 2): 4 kGy • Maximum dose at syringe level (Positions 5, 13, 14, and 15 in Figure 2): 4 kGy • Maximum dose at any point of the plastic box of the tub or top of the Tyvek lid (Positions 1, 6, 7, 8, 9, 10, 11, and 12 in Figure 2): 4 kGy	Ozone concentration < 0.2 ppm for each measurement.
25 kGy	• Minimum dose under the Tyvek cover at any point of the sheet (Positions 2, 3, and 4 in Figure 2): 25 kGy • Maximum dose at syringe level (Positions 5, 13, 14, and 15 in Figure 2): 5 kGy • Minimum dose at any point of the plastic box of the tub or top of the Tyvek lid (Positions 1, 6, 7, 8, 9, 10, 11, and 12 in Figure 2): 25 kGy	Ozone concentration < 0.2 ppm for each measurement.
2 × 25 kGy	• Minimum dose under the Tyvek cover at any point of the sheet (Positions 2, 3, and 4 in Figure 2): 50 kGy • Maximum dose at syringe level (Positions 5, 13, 14, and 15 in Figure 2): 10 kGy • Minimum dose at any point of the plastic box of the tub or top of the Tyvek lid (Positions 1, 6, 7, 8, 9, 10, 11, and 12 in Figure 2): 50 kGy	Ozone concentration < 0.4 ppm for each measurement.
50 kGy	• Minimum dose under the Tyvek cover at any point of the sheet (Positions 2, 3, and 4 in Figure 2): 50 kGy • Maximum dose at syringe level (Positions 5, 13, 14, and 15 in Figure 2): 10 kGy • Minimum dose at any point of the plastic box of the tub or top of the Tyvek lid (Positions 1, 6, 7, 8, 9, 10, 11, and 12 in Figure 2): 50 kGy	Ozone concentration < 0.4 ppm for each measurement.

Table D. Acceptance criteria for dosimetry and ozone testing of syringe tubs.

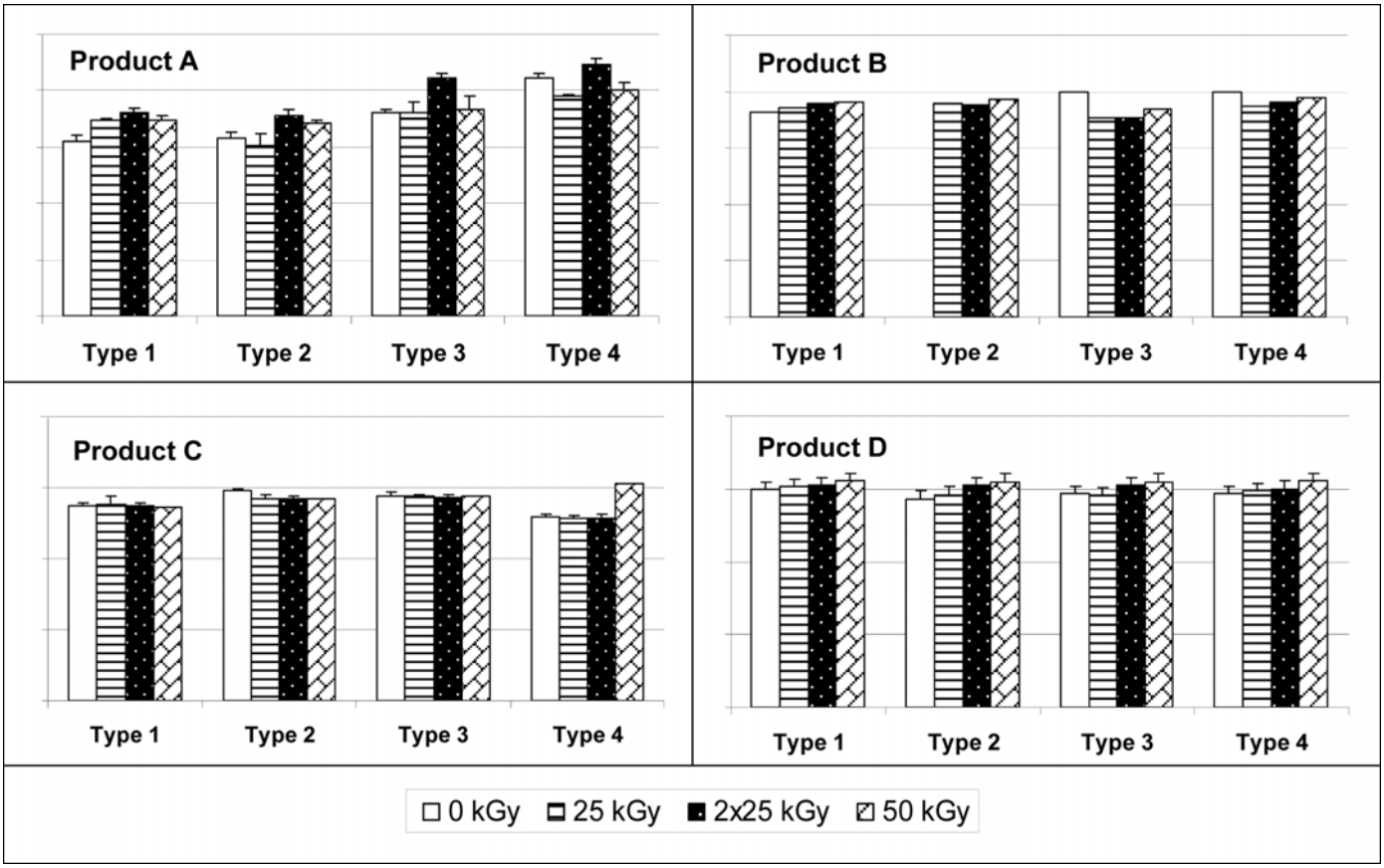


Figure 6. Protein drug products stability profile from E-Beam irradiated syringes (3-month, accelerated condition). Note: 1) Types 1-4 are different syringe types from different vendors. 2) In each syringe type group, the leftmost bar stands for the non-treated control (0 kGy). 3) Only accelerated stability data at the 3-month time point are shown.

both incubation conditions, demonstrated no adverse impact on product stability from all types of E-Beam treated syringes when they were compared to the untreated controls - *Figure 6*.

The limitation of this study was that the E-Beam irradiated syringes were filled several days after dosing and the concern was that the Ozone may have dissipated from the treated syringe tubs. In routine manufacturing operations, the treated syringe tubs will be opened and the syringes re-oriented and filled immediately after E-Beam irradiation. The filled syringes will then be immediately stoppered and re-nested. To address these concerns, a further evaluation of the potential impact of residual Ozone concentration on drug product quality was conducted in a separate study, as described below.

Product Impact from Ozone Introduced in Syringe Headspace

This follow on study was designed to evaluate the stability of drug products after exposure to various concentrations of Ozone (0, 0.2 - 0.5, 1.8 - 2.2, and 18.0 - 22.0 ppm), which were introduced into the headspace of pre-filled syringes in order to simulate the effect of filling syringes immediately after dosing and Ozone build up within the syringe barrel. The results from stability indicating assays from the six-month stability time point at 2 - 8°C showed no significant impact on drug product quality was observed for the samples treated at Ozone concentrations of 0.2 - 0.5 and 1.8 - 2.2 ppm when compared to the untreated controls. All results were well within the products stability profile and met acceptance specifications. At much higher Ozone concentration of 18.0 - 22.0 ppm, one drug product started to show higher oxidation rate after one week incubation at 2 - 8°C when compared to its untreated controls. Nonetheless, that level of Ozone (18.0 - 22.0 ppm) was found to be more than 200 times higher than the highest Ozone concentration measured inside syringe tubs after E-Beam irradiation at the vendor site.

Conclusion

A KT analysis was performed to evaluate the selected key criteria on the five possible process compatible E-Beam designs. Based on this KT analysis, the Design 1 system received the highest score and was recommended for further operational evaluation on the robustness and efficacy.

Results from the dosimetry mapping and Ozone concentration study showed that the residual irradiation dose and Ozone level inside a syringe tub were extremely low post-treatment. Thus, E-Beam technology was determined to be amenable for subsequent product impact evaluations of the recommended E-Beam Design - *Figure 1*. The subsequent product impact evaluations focused on extractable profile of E-Beam irradiated syringes, irradiated syringes impact on

filled protein drug product, and the effects of Ozone oxidation to the long-term stability of drug products. Up to six months stability results from these product specific stability studies effectively demonstrated that E-Beam irradiated syringes and low levels of Ozone generated through the E-Beam sterilization process had no impact on drug product quality. The data to date supports the suitability of E-Beam sterilization technology for protein drug products in the PFS filling process.

References

1. Allison, D.G., Mohammad, S., "Traditional or Non-traditional Approaches to the Sterilisation of Medical Devices," *Business Briefing: Medical Device Manufacturing and Technology,* 2002, pp. 42-46.
2. Hoxey, E., Thomas, N., "Gaseous Sterilization," *Principles and Practice of Disinfection, Preservation and Sterilization*, 3rd edition, Russell, A.D., Hugo, W.B., Ayliffe, G.A.J., Eds. 1999; pp. 703-732.
3. http://www.ddkscientific.com/.
4. General Guideline for UVGI Air and Surface Disinfection Systems. International Ultraviolet Association: 2005.
5. Woolston, J., "Sterilisation Technology Choices during Product Design and Development." *Medical Device Technology,* 2001**,** 12, (2), pp. 18-21.
6. Elston, C., "Helping Packaging Stand Up to Sterilization," *Pharmaceutical and Medical Packaging News,* December 2005.
7. Barnard, J.W., "Factors Influencing Equipment Selection in Electron Beam Processing," *Nuclear Instruments and Methods in Physics Research B* 2003**,** 208, pp. 98-101.
8. Sadat, T., Malcolm, F., "A New E-Beam Application in the Pharmaceutical Industry," *Nuclear Instruments and Methods in Physics Research B,* 2005**,** 240, pp. 100-104.
9. Sadat, T., Huber, T., "E-Beam-A New Transfer System for Isolator Technology," *Radiation Physics and Chemistry,* 2002**,** 63, pp. 587-589.
10. van Lancker, M., Bastiaansen, L., "Electron-Beam Sterilization: Trends and Developments, *Medical Device Technology,* 2000**,** 11, (4), pp. 18-21.
11. http://www.kepner-tregoe.com/.
12. *Gray (Gy) is the SI unit of Measurement of Absorbed Irradiation. One Gray (Gy) is the Adsorption of One Joule of Radiation Energy by One Kilogram of Matter, CRC Hand Book of Chemistry and Physics***,** 77th edition, pp. 1-20.
13. "Choice of Sterilizing Dose," Par. 4.2. ed., European Standard EN 552, 1994.
14. "Establishing the Sterilization Dose. ISO 11137-1 ed.; Organization, I. S., Ed. 2006; Vol. par. 6.2.2.
15. GEX-Technical-Team, http://www.gexcorporation.com/tech.html, Post-Irradiation Heat Treatment of B3 Dosimeter Products.

Acknowledgements

The authors would like to thank the following colleagues for their contribution to the E-Beam technology evaluations: Rob Swift, Michael Denzer, Sharon Wu, Grace Chu, SungAe Park, Athena Nagi, and Kate See. The authors also are grateful for the management support from Angel Aquino and Steven Ruhl.

About the Authors

Xiaogang Pan is a Scientist in Drug Product and Process Development at Amgen Inc. His responsibilities include developing and characterizing commercial processes for drug products, supporting commercial production, and evaluating new fill/finish manufacturing technology. He is a member of the Drug Product and Process Development Aseptic Processing Technology Leadership Team. Previously, he worked as a process design engineer focusing on pharmaceutical manufacturing process/facility design. He received his PhD in pharmaceutics from Ohio State University. He can be contacted by telephone: +1-805-447-6660 or by email: xiaogang.pan@amgen.com.

Amgen Inc., Mail Stop 30W-3-A, One Amgen Center Dr., Thousand Oaks, CA 91320, USA.

Xiangning (Sean) Deng is a Senior Scientist in Drug Product and Process Development at Amgen Inc. His main responsibilities include evaluating fill/finish manufacturing technologies for Amgen and supporting the manufacturing of Amgen drug products. He is now leading the evaluation of E-Beam, Isolator, and Automated Visual Inspection technologies for Amgen's clinical and commercial manufacturing facilities. He has worked in the diagnostic and biopharmaceutical industry for seven years, focusing on manufacturing process development, product quality improvement, and technology transfer for commercial products. His education includes a PhD in molecular biology from University of Delaware, an MBA from Long Island University, and postdoctoral training at University of California, Davis. He can be contacted by telephone: +1-805-313-6390 or by email: xdeng@amgen.com.

Amgen Inc., Mail Stop 30W-3-A, One Amgen Center Drive, Thousand Oaks, CA 91320, USA.

Ka Kit (Michael) Lee is a Scientist in the Drug Product and Process Development at Amgen Inc. He is responsible for technology evaluation, including impact on drug products, packaging components, equipment, and the aseptic filling processes. He participates in designing evaluation protocols for experiments executed both internally and at other facilities. Lee also is involved in the design of Amgen fill/finish facilities. He received his PhD in chemical engineering

from University of California, Irvine. He can be contacted by telephone: +1-805-447-9367 or email: kaklee@amgen.com.

Amgen Inc., Mail Stop 30W-3-A, One Amgen Center Dr., Thousand Oaks, CA 91320, USA.

Thomas O'Sullivan is a Principal Engineer in Drug Product and Process Development at Amgen Inc. His current responsibilities include design support for Amgen's fill/finish and process support for commercial and late-stage clinical products. He is part of the cross functional team responsible for the evaluation design and implementation of new technologies in Amgen's commercial fill/finish facilities. Sullivan has more than 24 years of industry experience, including expertise in decontamination and sterilization systems, aseptic formulation, and fill/finish processing of SVPs, process and technology evaluation and transfer. He holds a BA in biological sciences from Manhattanville College in Purchase, New York. He can be contacted by telephone: +1-401-392-9768, or by email: tosulliv@amgen.com.

Amgen Inc., Mail Stop: ARI, AR1-6-2B, 40 Technology Way, West Greenwich, RI 02817, USA.

Edwin Torres is a Senior Engineer at Amgen Manufacturing Limited at Juncos, Puerto Rico. He has nine years of experience in the medical device and pharmaceutical industry. In his current role, Torres has the responsibility for process troubleshooting, assessment of critical process parameters, and identifying new technologies for aseptic filling of syringes and vials. He also has experience in the areas of Injection Molding, Equipment Maintenance, and E-Beam. He received his BS in mechanical engineering from University of Puerto Rico – Mayagüez Campus in 1999. He can be contacted by telephone: +1-787-367-9534 or by email: edtorres@amgen.com.

Amgen Manufacturing Limited, P.O. Box 4060, Mail Stop: AMLT11B-109, Juncos, Puerto Rico 00777, USA.

Adrian Distler is a Director of Drug Product and Process Development at Amgen Inc. His responsibilities include leading a group of engineers and scientists that perform process development and characterization, technology transfers, and manufacturing support of protein-based drug product for proteins. His expertise is in late-stage commercialization, process scale-up and transfers as well as technology evaluation. Distler has worked in the Process Development organization for 12 years on a variety of molecules and various team lead roles. He holds a BS in physics from the University of Cincinnati. He can be contacted by email: adistler@amgen.com.

Amgen Inc., Mail Stop 30W-3-A, One Amgen Center Dr., Thousand Oaks, CA 91320, USA.

Narinder Singh is a Director of Drug Product and Process Development at Amgen Inc. He currently heads a group of scientists and engineers that is primarily responsible for providing drug product support to Amgen's commercial and late-stage products. His group develops and characterizes commercial processes for drug products, performs technology transfer to manufacturing sites, and supports the commercial production. His group also is responsible for new manufacturing technology evaluation for implementation at commercial manufacturing sites. Singh has worked in a variety of roles within Operations at Amgen for more than 11 years. He holds an MS and BS in biochemical engineering and biotechnology from Indian Institute of Technology, Delhi, an MS in chemical engineering from University of Houston, and an MBA from UCLA Anderson School, Los Angeles. He can be contacted by telephone: +1-805-313-1737 or by email at nsingh@amgen.com.

Amgen Inc., Mail Stop 92-2-A, One Amgen Center Dr., Thousand Oaks, CA 91320, USA.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
November/December 2008, Vol. 28 No. 6

Case Study: Beta-Lactam Decontamination and Cleaning Validation of a Pharmaceutical Manufacturing Facility

This case study will review the main items of a decontamination protocol for the renovation of a beta-lactam production facility into a non-beta-lactam production facility.

by Hisao Takahashi, PE, Hiroshi Sakai, and Dr. Daniel H. Gold

Introduction

A question frequently asked by former producers of beta-lactam antibiotics is: Can a facility that produced beta-lactams be successfully decontaminated and renovated for the production of non-beta-lactams, meeting all regulatory expectations after conversion for absence of detectable beta-lactam residues?

Toyama Chemical Co., Ltd. planned to convert a synthesis factory (factory no. 6) into a clinical supplies drug substance and an initial active pharmaceutical ingredient manufacturing facility that would meet cGMP regulations. However, there was a potential for cross-contamination with beta-lactams, because the synthesis factory had been in use for a number of years producing Cephalosporin entities. There were five beta-lactam entities previously produced in this factory, code named P15, P16, P23, P24 and DX-B.

To beneficially use this factory, Toyama developed a comprehensive decontamination protocol. After preparing the protocol, Toyama contacted the US FDA for discussion of the proposal and agreement of the procedures to be

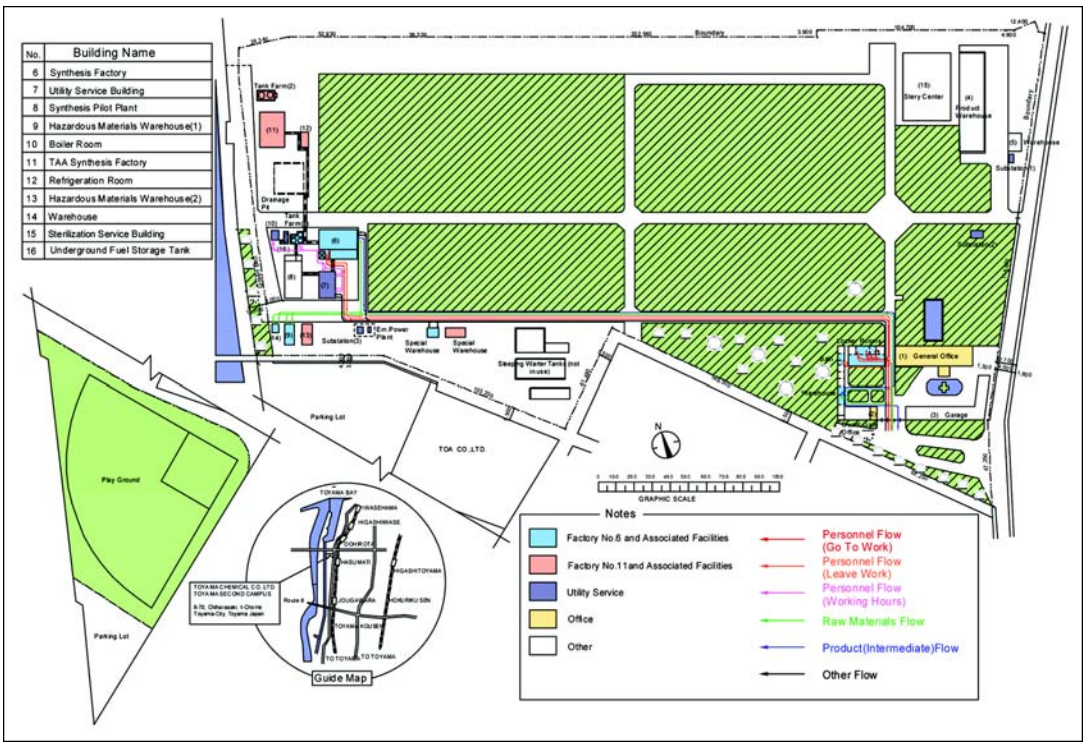


Figure 1. Factory profile and personnel, material, and product flows.

used and the acceptance criteria to be used to justify the facility for subsequent use.

General Layout and History

Toyama purchased an unused site of a grain factory in July 1981. It has an area of 100,200 m^2, 86,000 m^2 of which is used as a factory site, 12,900 m^2 of which is used as a play ground site, and 1,300 m^2 of which is a gate site.

When Toyama acquired the site, almost all of the buildings were on the verge of collapse. The only surviving buildings from the original purchase were the general office, a guard gate office, a warehouse, and a garage - *Figure 1*. All other buildings on the site were built after 1983.

Five buildings were built during the first construction phase: a steel frame fireproof synthesis factory (factory no. 6) comprising three floors and a tank farm, a synthesis pilot plant, a utility service building, a boiler room, and a hazardous materials warehouse. These five buildings were completed by July 1984. The Synthesis Factory was built for the purpose of producing beta-lactam intermediate P23. The tank farm was made up of a solvent tank and two waste liquid tanks for the synthesis factory.

In the second phase of construction, three buildings were completed by September, 1987. They included a steel frame fireproof non-beta-lactam drug substance Synthesis Factory that has two floors, a refrigeration room, and a hazardous materials warehouse.

The synthesis factory was remodeled into another beta-lactam intermediate P24 special factory and a small warehouse was completed in February, 1993.

Levels of Contamination

The expected level of contamination with beta-lactams throughout this campus was assessed based upon the degree of beta-lactams exposure and the flows. Following an evaluation of the degree of exposure and of whether cross-contamination could likely occur due to the flows, such as personnel, material, product flows, and air circulation in the facilities/buildings at this campus, a contamination risk assessment model as illustrated by Figure 2 was used to determine the level of possible contamination.

Three levels of contamination were defined:

- Level I – facilities/buildings that have handled beta-lactams
- Level II – facilities/buildings that haven't handled beta-lactams. However, there were some levels of personnel, material, or air circulation flows into these areas. Level II was further sub-divided into two classifications depending upon the facility/building use after decontamination:
  - Level IIa – After decontamination, these facilities/buildings are intended to be utilized the same as before.
  - Level IIb – After decontamination, these facilities/buildings are intended to be put to different use than before.
- Level III – facilities/buildings that haven't handled beta-lactams and there weren't any personnel, material, or product flows into these.

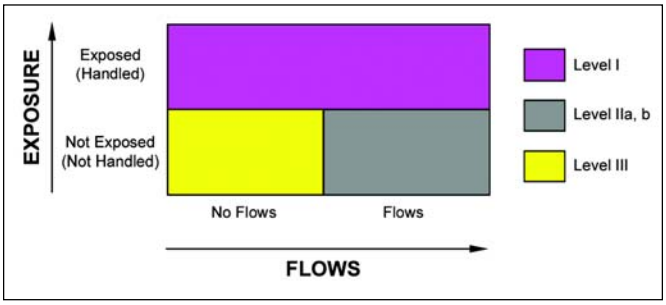


Figure 2. Levels of contamination.

Dismantling and Cleaning Procedures

Following completion of the contamination risk assessment, Toyama considered it necessary to decontaminate all of the facilities/buildings at this campus that might have been contaminated by personnel, material, product flows, or air circulation. Specific decontamination procedures were developed based upon the exposure risk estimate. For example, dismantling and cleaning procedures for Level I were as follows:

High Exposure: Level I (Synthesis Factory, Warehouses, etc.)

Architectural

- Floors – After decontaminating with reagent solution, concrete floors were coated with epoxy paint. Steel floors and structural steel were painted with a synthetic oil compound.
- Walls-Exterior – Autoclaved Light weight Concrete (ALC) or concrete, are materials of construction that have considerable porosity. Therefore, they were finished with epoxy paint after decontaminating with reagent solution.
- Walls-Interior – Interior walls consisted of gypsum board, pre-decorated calcium silicate incombustible board, and aluminum sash. Gypsum board was renewed since it becomes moist with decontamination solution. Pre-decorated calcium silicate incombustible board and aluminum sash were decontaminated with reagent solution.
- Ceilings – Some of the ceilings were constructed of gypsum board. Therefore, these ceilings were renewed for the same reason. Other ceilings were made of steel. These ceilings were decontaminated with reagent solution and finished with synthetic oil compound paint.
- Roof – The building roof was made of roofing material that was porous and absorbent. Therefore, the roof was removed and new roofing installed.
- Structural members – Structural members made of steel were decontaminated with reagent solution and then finished with synthetic oil compound paint.

Process Equipment

- Process, process support – Beta-lactam equipment pre-decontaminated with reagent solution was dismantled and further decontaminated with reagent solution (e.g.,

reactors, hold tanks, centrifuges, filters, dryers, and pumps). All equipment considered unnecessary and all beta-lactam piping and valves were removed. Additionally, all gaskets and seals were exchanged for new.
- Utility – Utility system exteriors, such as air and steam, etc. were decontaminated with reagent solution. All gaskets and seals were exchanged for new.

HVAC

- HVAC systems: Exhaust fans, heating and cooling systems, filters, local spot exhaust systems, and piping and ducting that were installed in the synthesis factory were judged to be potentially contaminated with beta-lactams. These HVAC systems are very complicated and impracticable to decontaminate. They were removed.

Insulation

- Insulation for the process equipment and piping also has the potential for contamination with beta-lactams. It was judged impracticable to decontaminate the insulation because it is highly absorbent. All of the insulation was removed.

Electrical Facilities

- Power distribution, control system, paging system, and fire alarm system installed in the synthesis factory were replaced.
- Conduits were replaced and electrical wires rerun.
- Explosion type lighting and outlets were decontaminated with reagent solution. However, regular (non-explosion) type lighting and outlets were replaced.

Dumb Waiter, Documents, and Spare Parts

- A dumb waiter basket, a roll-up motor, and a roll-up rope were renewed since these parts of a dumb waiter are impracticable to decontaminate. The dumb waiter pit is made of concrete and walls and a roof are made of ALC. These architectural materials were decontaminated with reagent solution and finished with epoxy paint.
- Documents and used spare parts were removed.

Cleaning Agents

Toyama carefully examined the reagent solution for cleaning. At the start of the examination, Toyama decided to refer to a literature article reporting procedures for decontamination of penicillin manufacturing facilities in Brazil.[1] According to this literature report, an aqueous solution of dilute NaOCl, NaOH, and surfactant SDS was found satisfactory as the reagent solution for penicillin decontamination. Toyama examined whether this reagent solution had similar effects on the Cephalosporin-type beta-lactams that were the targets of our cleaning operation.

The components of the solution were thought to be related to the actions shown below. Examination was conducted to confirm these modes of action and to establish the appropriate concentration of each component for the specific entities to be decontaminated at Toyama:

- NaOCl: Decomposition of beta-lactam compounds.
- NaOH: Decomposition and prompt dissolution of beta-lactam compounds.
- Sodium Dodecyl Sulfate (SDS): Surface-active effects.

As a result, the following reagent composition was found to be best suited for decontamination. Toyama found the intended reagent could destroy the beta-lactam ring in the mix of concern by spraying this reagent solution for 15 seconds or simply wiping with a cloth wetted with the solution. Specific compositions of reagent solution Toyama used:

- NaOCl: At the concentration of 0.5 vol. %
- NaOH: At the concentration of 0.1 %
- SDS: At the concentration of 1.0 %

Residue Sampling

After beta-lactam ring decomposition treatment, it was necessary to test the effectiveness of treatment. The residue sampling procedure was as follows:

Each designated sampling location (100 cm^2) was wiped with a clean sampling swab stick containing 1/15 mol/L phosphate buffer (pH 7.0) by an operator who had been trained in swab sampling methodology. Sampling locations were designated for each facility/building, such as architectural, process equipment, electrical facilities, etc.

To determine the recovery of beta-lactams from typical facility/architectural materials, if present, typical test surfaces were impregnated with low levels of each of the beta-lactams. When these surfaces were impregnated with 200 ng of each entity of concern the recovery was more than 70% except for concrete and ALC.

Therefore, to assure decontamination success, all concrete and ALC surfaces were coated with epoxy paint after decontamination to provide a positive, leak-proof seal. Toyama confirmed that none of the beta-lactams of concern would bleed through an epoxy coated concrete surface seal. This confirmation was obtained as outlined below.

- Monitoring Test 1: Concrete test pieces were surface impregnated with the five beta-lactams, then decontaminated in the same manner as the facility, followed by epoxy painting. Samples were scheduled to be taken at 0, 1, 2, 3, 6, 12, 18, 24, 36, 48, and 60 months. Assay methods were to be the same as those used in the decontamination assessment.
- Monitoring Test 2: Test 1 was designed to simulate actual conditions. However, if decontamination were fully effective, Test 1 would not show a possible bleed through effect. So, Test 2 also was applied. In Test 2, concrete test pieces were surface impregnated with five beta-lactams, followed by epoxy painting without decontamination. Sampling points and assay methods were to be the same as with Test 1.
- Monitoring at facility: At the request of the FDA, samples were to be taken for assessing a possible bleed through epoxy coated concrete at high traffic locations in the

	P15	P16	P24	P23	DX-B
Test Method	LC/MS/MS	LC/MS/MS	LC/MS/MS	Micro Bioassay	LC/MS/MS
Detection Limit (ng/cm^2)	0.6	0.6	0.6	1.0	0.6

Table A. Test method and detection limit of beta-lactams.

facility at 3, 6, 9, 12, 18, 24, 36, 48, and 60 months after completion of decontamination. All surface monitoring tests were negative. The results for 60 months of testing were finished successfully in 2004.

Analytical Procedures

As test methods, the microbiological assay and the LC/MS/MS method were established based on analytical method validation - *Table A*. Based upon the analytical procedure coupled with the demonstrated sampling recovery, Toyama showed the five beta-lactams of concern would be detected on swabbed surfaces if present at 0.6 ng – 1 ng/cm^2 (P15, P16, P23, P24 and DX-B).

Acceptance Criteria

The Toyama decontamination criteria were:

No residual beta-lactam agent shall be detected by the microbiological assay and the LC/MS/MS method that can be devised.

The Result of Decontamination

Table B shows assay results obtained after the initial decontamination of Level I and Level II facilities. In total, 1,134 samples were taken from the synthesis factory after decontamination. For the 25 samples that still tested positive, Toyama decontaminated the entire room and/or area where each of the positives occurred and took 278 samples after that. These 278 samples were all negative. From the other Level I facilities, 143 samples were taken. No positive results were obtained. In summary, 1,277 samples were taken from Level I facilities after decontamination. Of these, 25 samples tested positive.

In accordance with the protocol, re-decontamination was required for the facility/equipment in which the positive samples were taken. After the re-cleaning, a double sampling program was implemented for 278 additional samples in total. No further positive test results were found.

From Level II facilities 178 samples were taken after decontamination. One sample point was positive. It was in the utility service building. Re-decontamination was required for the area in which the positive sample was taken in the same manner as for Level I. After the re-cleaning, additional 28 samples were all negative.

As expected, all of the 198 samples taken from Level III facilities were negative prior to execution of decontamination procedures. Therefore, Level III facilities were thought not to

Level I Facilities			
Facility	**Number ofSamples [a)]**	**Number of Detected**	**Number ofSamples [b)]**
Factory No.6	1,134	25	278
Tank Farm (1)	76	0	-
Beta-Lactam Warehouse	37	0	-
Utility Service Building	30	0	-
Total	1,277	25	278
Level II Facilities			
Facility	**Number ofSamples [a)]**	**Number of Detected**	**Number ofSamples [b)]**
Utility Service Building	83	1	28
Boiler Room	29	0	-
Locker Room	50	0	-
Bath	16	0	-
Total	178	1	28
Level III Facilities			
Facility	**Number ofSamples [c)]**	**Number of Detected**	**Number ofSamples [a)]**
Non-Beta-Lactam Synthesis Pilot Plant	60	0	-
Non-Beta-Lactam Synthesis Factory	44	0	-
Utility Room and Three Storehouse	13	0	-
General Office	12	0	-
Warehouse No14	8	0	-
Hazardous material Warehouse (1)	6	0	-
Others	55	0	
Total	198	0	
All Total	**1,653**	**26**	**306**

a) Number of samples taken after decontamination
b) Number of samples taken after re-decontamination
c) Number of samples taken to confirm no-contamination

Table B. Assay results of decontamination.

	P15	P16	P24	P23	DX-B
Test Method	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
Detection Limit (ng/g)	20	5	5	5	10

Table C. Test method and detection limit of beta-lactams in drug substance after decontamination.

need decontamination.

Overall, a total of 26 samples out of 1,653 samples were detected as positive after initial decontamination. An additional 306 samples was taken after re-decontamination. It was confirmed that all of those additional samples were negative.

After decontamination, Toyama confirmed absence of cleaning reagent residues by determination of colorimetric method and total organic carbon.

The Result of Beta-Lactam Agents in Drug Substance After Decontamination

The initial three lots of API manufactured after decontamination were tested for absence of beta-lactams. Thereafter, one lot per year of drug substance has been tested for absence of beta-lactams. All tests were found negative. The results for 60 months of testing finished successfully in 2004. Beta-lactam levels of detection in the drug substance manufactured in Factory No.6 are shown in Table C.

Conclusion

Toyama considers the decontamination of beta-lactams at the synthesis factory a complete success. All samples taken after decontamination and re-decontamination or before decontamination at Level III facilities were negative. Facility post-decontamination monitoring results also have been negative.

Moreover, drug substance manufactured in the facility after decontamination has shown no evidence of any of the prior beta-lactams at detection levels from 5 to 20 ng/g.

The US FDA commended Toyama for a job well done. The US FDA staff informed Toyama that the decontamination protocol program and the procedures applied in execution of that program met all applicable GMP standards.

Reference

1. Hakimipour, Fred, "Penicillin Decontamination Procedures for Pharmaceutical Manufacturing Facility," *Pharmaceutical Technology,* June 1984.

About the Authors

Hisao Takahashi, PE is a Director and General Manager of Industrial Technology Department for Toyama Chemical Co., Ltd. in Japan. He received an MS in chemical engineering and has been working on pharmaceutical process and engineering projects for more than 25 years. He was the project leader for several process developments of new drugs, pharmaceutical manufacturing facility engineering and validation, and has specialized in process development, technology transfer, facility design, and qualification and process validation. He specializes in decontamination and cleaning validation, containment, and control of pharmaceutical facilities. He can be contacted by telephone at: +81-76-431-8235 or by e-mail at: hisao_takahashi@toyama-chemical.co.jp.

Toyama Chemical Co., 2-4-1, Shimookui Toyama, 930-8508 Japan.

Hiroshi Sakai is a Research Manager of the QAC Department at the Toyama Chemical Co., Ltd. He graduated from Toyama National College of Technology. He has experience as the head of the analytical research laboratory and the general manager of Quality Control Department at the Toyama Chemical Co. His research experience includes physicochemical property and metabolism for the new drug product at the laboratory and includes organic chemistry as a research student of the University of Tokyo. He can be contacted by telephone at: +81-76-431-8252 or by e-mail at: hiroshi_sakai@toyama-chemical.co.jp.

Toyama Chemical Co., 2-4-1, Shimookui Toyama, 930-8508 Japan.

Dr. Daniel H. Gold is the President of D.H. Gold Associates, Inc. His company specializes in compliance issues, including facility design and qualification, process transfer, process computer systems validation, aseptic processing, clinical supplies, laboratory management systems, employee certification programs, and DMF preparation and maintenance. Facility and systems audits are a particular specialty. Formerly, Dr. Gold was Vice President of Quality at Par Pharmaceuticals and Senior Director at Lederle Laboratories. Dr. Gold received his BS from Brooklyn College and his PhD in physical chemistry from the Polytechnic Institute of New York. Author of numerous papers and patents, he is currently a member of FDA's Pharmaceutical Sciences Advisory Manufacturing Subcommittee. He can be contacted by telephone: +1-201-845-7171 or by email: dhg@dhgoldassociates.com.

D. H. Gold Associates, Inc., 151 W. Passaic St., Suite 7, Rochelle Park, New Jersey 07662, USA.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
November/December 2008, Vol. 28 No. 6

A Risk-Based Approach to Defining Levels of Protection within API Facility Design: The Concept of Briefly Exposed (Briefly Open)

This White Paper presents the Briefly Exposed (Briefly Open) concept in the context of Intermediate and API processing based on adopting a risk-based approach as outlined in the API Baseline® Guide.

by Stan Newberger and Dr. Trish Melton

Introduction

This White Paper is written in support of the ISPE Baseline® Guide on Active Pharmaceutical Ingredients (API), in which a new concept, Briefly Exposed (Briefly Open) was introduced. The discussion will expand on the concept, provide further clarification, and demonstrate how to use the concept in practice. This White Paper will focus on the Briefly Exposed (Briefly Open) concept in the context of Intermediate and API processing based on adopting a risk-based approach.

Background

The ISPE Baseline® Guide: Active Pharmaceutical Ingredients, published in June 2007, is a revision and update to the ISPE Baseline® Guide: Bulk Pharmaceutical Chemicals, published in June 1996. In the original Guide, the concept of a process step being a critical process step either due to chemistry or due to physical contamination was presented. The tools to control physical contamination also were given and presented as the Levels of Protection. It was recognized that the Levels of Protection, identified and defined in Chapter 2 of the original Guide as Level I – General, Level II – Protected, and Level III – Controlled, also are related to the criticality of the step. With that as a basis, Table 2-1 Recommended Level of Protection was developed - *Figure 1*.

Figure 1 recognizes two conditions: Not Exposed (Closed) or Exposed (Open). There is not an intermediate condition of opening a process for a short amount of time (Briefly Open).

Figure 1 (with FDA agreement), was attempting to give manufacturers an option of utilizing the Protected category (Level II), which allows for drug substance protection in certain circumstances without having to use the more highly restrictive Controlled condition (Level III). Experience shows that many manufacturers did not take advantage of this Protected category in practice, because they felt that there would be greater risk associated with it. This low use of Level II indicated a lack of understanding of the risks which were or were not present.

The FDA suggests that manufacturers understand the ultimate risk to the patient and focus on the areas of greatest patient risk. During the design of API facilities, there needs to be an awareness of which areas represent the greatest risk to the API and the greatest risk to the patient. This risk-based approach was integrated into the new Baseline® Guide and a third condition was added to the former Table 2-1: Briefly Exposed (Briefly Open). It is shown as Figure 2.9: Recommended Levels of Protection - *Figure 2*.

This new concept allows manufacturers another degree of freedom in their operations. They will be able to briefly open their processes for various reasons (sampling, adding ingredients) for short time periods and under certain circumstances and to apply the most appropriate levels of protection (Level I, II, or III) based on risk mitigation. An assessment of the risk to the API and ultimately to the patient is an appropriate method for manufacturers to establish what those circumstances are.

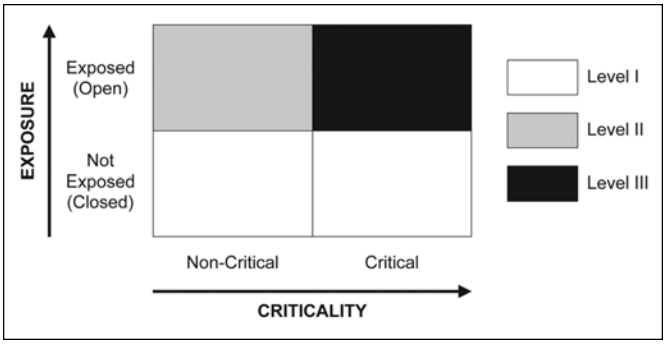


Figure 1. Recommended Level of Protection (BPC Baseline® Guide, Table 2-1).

External Contamination

Potential contamination may contact the API or intermediate from sources that are either internal or external to the processing equipment. It is expected that risks to the API and intermediate from both of these sources will be managed and appropriately mitigated.

External contamination comes from the external environment to which the API or intermediate is exposed. An operation is exposed (open) if the API or intermediate is exposed to the environment during the processing step, or not exposed (closed) if the API or intermediate is not exposed to the environment.

Where external contamination can impact the impurity profile of the API or intermediate, it is termed critical. Therefore, this use of the word 'critical' is analogous to the use of the word when referring to critical parameter or critical unit operations.

Levels of Protection

The concept of Levels of Protection was introduced as a "tool" in the original Guide to aid in determining how extensive the protection from the environment, and potential contaminants, an API or intermediate would need, i.e., does it need the same amount of protection:

- From the moment the process starts until the very end?
- Through every step (critical step versus non-critical step)?

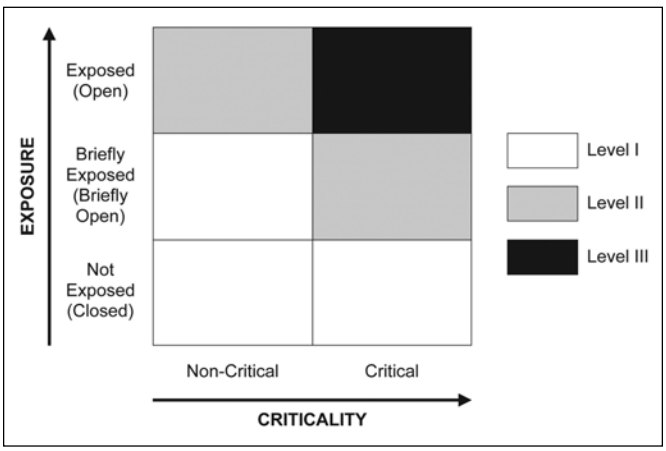


Figure 2. Recommended Levels of Protection (API Baseline® Guide, Figure 2.9).

- Regardless of the final intended use of the API (i.e., foot powder versus oral dosage versus injectable)?

The original Guide and the revised Guide both define three different Levels of Protection: Level I – General, Level II – Protected, Level III – Controlled. The definitions of each of these Levels of Protection are in Chapter 2 of the Guides. Each of these levels will have a specific economic and operational impact on the manufacture of the API. Each also will introduce a different risk of contamination to the API or intermediate. Table 2-1 (1996 Guide) and Figure 2.9 (2007 Guide) give the manufacturer a way to determine the appropriate Level of Protection depending on whether the operation is occurring during a critical or non-critical unit operation as well as the degree of exposure of the operation.

The main difference between the original version of the Levels of Protection Table and the newer version is the addition of a Briefly Exposed (Briefly Open) option. In addition, the new Guide clarifies that criticality should be reviewed at the unit operation level. This approach highlighted the usefulness and usability of the Level II category of protection when a manufacturer is able to fully define the risk scenario.

Why Briefly Exposed?

Exposed (Open) and Not Exposed (Closed) are definitive terms. The process is either open or its not. However, is the risk of contamination the same when a vessel is open for eight hours, as it is when it is opened for one hour, as it is when it is opened for a few seconds? Obviously, the risk will be different in each case. The risk to the API or intermediate also will be different in each case depending on which method of protection is utilized. Ultimately, the risk to the patient could also be different depending on all of the above as well as the intended patient use.

Recognizing that a very brief (brief time) opening of a process to perform a specific activity could present an economic and operational advantage over a completely closed process, and recognizing that a very brief (brief time) opening of a process within either a non-critical or a critical unit operation could be protected to allow a low risk to the API or intermediate, the Briefly Exposed (Briefly Open) option was added.

The Guide states that Briefly Exposed (Briefly Open) refers to an opening of a "few seconds." The few seconds is the time that it is envisioned to open a port on the process vessel and to either add an ingredient or to take a sample quickly. If the operation is not a part of a critical unit operation, Figure 2.9 (Figure 2) shows that this could be accomplished with a Level I – General level of protection. If the operation is a part of a critical unit operation, Figure 2.9 (Figure 2) shows that this could be accomplished with a Level II – Protected level of protection.

The Briefly Exposed (Briefly Open) option was added because it is presumed to be a very low risk option that will have a positive impact on the manufacture of APIs from an economic and operational perspective. However, each manu-

facturer still needs to assess the risk for each of their specific scenarios, always keeping in mind the risk to the patient.

Risk to the Patient versus Risk to the Operator

In considering risk, it is important that the consequences of concern are highlighted and the level of risk is objectively assessed. In that way, the risk assessment can be shown to be both repeatable and reliable, for example:

- Repeatable – if the same person conducted the risk assessment at two different times, assuming the situation had not changed, then the risk level would be the same.
- Reliable – if two different people conducted the risk assessment at the same time, but separately, then the risk level would be the same.

In terms of the concept of Briefly Open (Briefly Exposed), it is important that the level of risk is objectively assessed in terms of the risk to the patient. However, exposure of a process to the surrounding environment also can cause risks to personnel working in the area and environmental risks. The intent of this White Paper is to only cover the risk to patient through impacting product quality.

Risk-Based Approach

In Chapter 3 of the revised Guide, a risk assessment approach was suggested. It was based on using risk decision flowcharts which themselves were developed considering specific risk scenarios applicable to the manufacture of APIs and their intermediates. Figure 3.2 in the Guide proposes a 4-stage process to assess and mitigate risk to patient. In summary:

- *Stage 1 Facility Designation* – the use of facility will impact the potential risks that can arise, e.g., dedicated versus multi-use facilities have different levels of potential cross contamination risk. The type of product being manufactured also should be considered.
- *Stage 2 Process Review* – the manufacturing process will follow a number of unit operations through the facility and each has the potential to introduce process risks, i.e., risks due to the process chemistry.
- *Stage 3 Contamination Review* – the facility and equipment (internal and external processing environment) has the potential to introduce physical contamination risks.
- *Stage 4 Impact Assessment* – the systems within a facility can be direct, indirect, or of no impact in terms of product quality and therefore, can also introduce risks to product quality which require mitigation.

External Contamination Review

The focus of this White Paper is the assessment of the risk of external contamination and to specifically review how the concept of Briefly Exposed (Briefly Open) can be used while not introducing any risk to patient. Therefore, this White Paper focuses on three different techniques to assess the level of risk from external contamination and to mitigate appropriately.

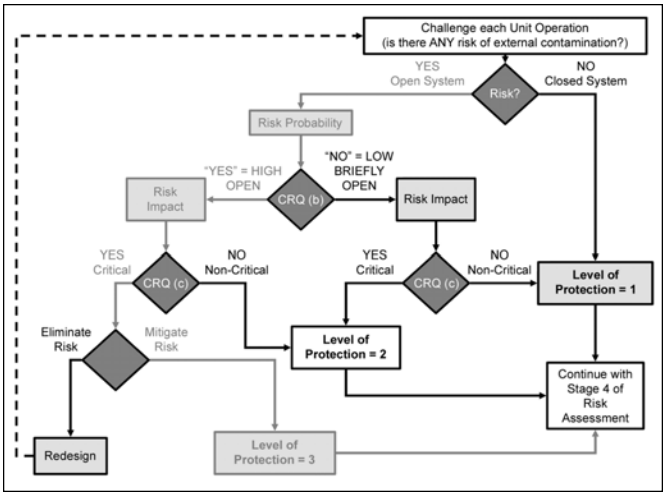


Figure 3. External Contamination Review Decision Flowchart (API Baseline® Guide, Figure 6.3).

More than one technique is proposed so that users can select the most appropriate one based on the data they have available. The following example scenario will be used with each technique and associated tool:

A crystallizer hand-hole needs to be open (exposed) for a short period of time (Briefly Open) in order to insert seed during the unit operation (crystallization).

Tool 1 – Decision Flowchart in API Baseline® Guide

This tool is introduced in the API Baseline® Guide. In terms of supporting Stage 4 of the risk assessment process (Contamination Review), Figure 3.6 (Figure 3) describes the decisions that need to be made in order to define the level of protection for a specific unit operation. By using contamination review questions (CRQ), it allows the user to determine if the operation is 'briefly open' and then, based on level of risk (and a further set of contamination risk questions), determine the most appropriate level of protection based on mitigating risk to patient - *Table A.* This decision flowchart technique supports three risk based decisions to identify the appropriate level of protection for a unit operation:

- Decision 1 – Any probability of risk?
- Decision 2 – Magnitude of probability of risk?
- Decision 2 – Impact of risk?

CRQ (b) – Risk Probability	CRQ (c) – Risk Impact
• Processing open during normal operations? • Large volume material charging each batch? • Extended period of open for process adjustments, charging, sampling? • External physical contamination can enter the processing environment?	• Q1. Multi-purpose facility (potential for cross contamination)? • Q2. Ability for external contaminants to impact the product impurity profile? • Q3. Could external contamination in the downstream process go undetected (and not be removed)?
• Yes to any of the above = HIGH risk probability • No to all the above = LOW risk probability	• Yes to Q3 = CRITICAL risk impact • Yes to Q1 or Q2 = Likely CRITICAL risk impact • No to all the above = Non-Critical risk impact

Table A. Contamination Review Questions (API Baseline® Guide, summary of Tables 3.3 and 3.4).

Phase One								Phase Two				
Failure Mode	Failure Effect	SEV	Causes	OCC	Controls	DET	Risk Score	Action Plan	SEV	OCC	DET	PRPN
< insert briefly open exposure risk – typically how contamination could enter the process >	< insert a description of the impact on the process >		< insert how this situation could occur >		< insert how this situation is detected >		< calc score >	< insert action >				
Scoring System												
SEV: 1 to 5 based on impact on product quality; 1 is low and 5 is high			**OCC:** 1 to 5 based on likelihood of contamination during failure mode (exposure); 1 is low and 5 is high				**DET:** 1 to 5 based on ability for the contamination to be detected; 1 is easily and 5 is not detected					

Table B. Briefly Open (Exposed) FMEA Template.

If the example scenario is used with Figure 3 and Table A, then the following is the result:

- Decision 1 – there is a risk of external contamination.
- Decision 2 – the risk is of a low probability due to time-scale of exposure.
- Decision 3 – the risk has a high impact due to unit operation criticality.

Based on these decisions the appropriate level of protection is Level II. In this case, the hand-hole is protected during exposure through use of a portable enclosure which surrounds the hand-hole. The operator uses a standard SOP which outlines how he must minimize contamination, e.g., clean gloves, clean paper overalls with no pockets.

Tool 2 – FMEA[1]

Failure Mode and Effect Analysis (FMEA) is a structured method for identifying and analyzing failure modes/defects within a process, system, or product. It is usually completed on a component by component basis and produces a Risk Priority Number (RPN) that allows prioritization of any subsequent action planning.

The FMEA technique develops mitigating actions to eliminate and/or reduce failure modes and/or their impact and/or increase detectability. It can be used to review potential scenarios which deliver external contamination into a process and therefore identify the appropriate level of protection for a unit operation.

Phase One

The initial part of the process involves failure mode or defect identification, description, and then scoring. In terms of the application of the FMEA technique to the assessment of external contamination risks via a briefly open operation, the following terms can be defined:

- *Failure mode* – all the various ways that external contamination can enter a process during the briefly exposed scenario should be listed – essentially these are all the things that could go wrong.
- *Failure effect* – for each identified failure mode, the consequence needs to be described in terms of the potential impact should contamination enter the process.
- *Severity (SEV) score* – a numerical score is assigned based on the failure effect. The scoring system for this type of analysis is shown in Table B. Severity is linked to the impact of the contamination on the process and therefore process criticality as previously discussed.
- *Causes* – for each identified failure mode, the cause should be explained. This needs to be a realistic scenario.
- *Occurrence (OCC) score* – a numerical score is assigned based on how likely the cause would be to occur. The scoring system for this type of analysis is shown in Table B.
- *Controls* – identify the current controls in place which would detect the failure mode.
- *Detection (DET) score* – a numerical score is assigned based on the controls and the ability for the failure mode to go undetected. The scoring system for this type of analysis is shown in Table B.
- *Risk Priority Number (RPN)* – this is a calculation: RPN = SEV × OCC × DET.

At this stage, the failure modes can be ranked according to RPN score. During facility design, the FMEA can be used as a design tool looking at the risks and associated risk priority number in the proposed facility design.

Phase Two

After the Risk Priority Number (RPN) has been calculated, the second part of the analysis can begin.

- *Action plan* – based on the RPN, define which failure modes require action and then define the action plan.
- *Rescoring* – based on the action plan, review whether the Severity (PS), Occurrence (PO), and Detection (PD) score has or will alter and calculate an updated Risk Priority Number (PRPN).

The reduction in risk priority number will be an indication of the mitigation of the risk. In terms of the briefly exposed scenario, it should indicate whether Level II or III solutions are required to reduce the risk priorty number to an appropriate level.

If the example scenario is used with Table B, the following results are shown. Table C highlights a number of failure modes for this situation: when the contamination is likely to impact the process and therefore the product and ultimately the patient.

Phase One								Phase Two				
Failure Mode	**Failure Effect**	**SEV**	**Causes**	**OCC**	**Controls**	**DET**	**Risk Score**	**Action Plan**	**PS**	**PO**	**PD**	**PRPN**
Potential briefly exposed scenario: crystallizer unit operation, addition of 100g of seed to the vessel via the manually opened hand-hole												
Debris above the exposed hand-hole	Debris enters the process	5	Shedding materials used in general facility and debris falls in during 5 second opening	3	Operator likely to see if anything drops into the hand-hole	1	15	Ensure temporary cover over the hand-hole is in place	5	1	1	**5**
Operator contamination as he opens the hand-hole and inserts the seed	Contamination enters the process	5	Operator has contamination on hands which comes off during 5 second operation	3	Likely contamination will be small and not easy to see	5	75	Operation SOP states that operator must wear gloves to conduct operation	5	1	1	**5**
		5	Operator drops something in the hand-hole by mistake in rush to complete operation	4	Operator likely to see if anything drops into the hand-hole	1	20	Operation SOP states that operator must wear a clean disposable suit (one use)	5	1	1	**5**
Potential contamination from the equipment used to weigh the seed	Contamination enters the process	5	General dispensing room used	3	Cleaning SOP in place including cleaning labels	1	15	None – check dispensing SOP is being followed	5	3	1	**15**
Potential contamination from the equipment used to weigh the seed	Contamination enters the process	5	Disposable equipment meant to be used once only	1	SOP in place to ensure new receptacle used	1	5	None – check charging SOP is being followed	5	1	1	**5**
Risk summary: The action plans reduce the risk priority numbers to an acceptable level. All the action plans will protect the unit operation and are all Level II solutions.												

Table C. Briefly Open (Exposed) FMEA Example.

All the actions proposed to mitigate the risks are to put protection in place during the dispensing and charging operation, in other words give the situation Level II protection.

Tool 3 – HACCP[1]

The Hazard and Critical Control Point (HACCP) technique can be used in a briefly exposed scenario. The technique is generally used to identify, manage, and control specific, detailed areas of the process. It relies on:

- the identification of critical control areas and within these critical control points
- the identification of hazards likely to impact these
- the management of critical control limits through definition of a method to identify and control the hazard.

The HACCP technique confirms actions which will manage a potential hazard within control limits. It can be used to identify the appropriate level of protection for a unit operation where there is the potential for external contamination by considering it to be a critical control area. The technique is in two parts:

- Part 1 – Identification of all critical control areas within the process
- Part 2 – Hazard analysis and control

During Part 1, the user should review the process flow diagram and consider each unit operation in turn. All unit operations which have the potential for chemical or physical contamination should be considered Critical Control Areas (CCA). In this way, a CCA can be defined as any combination of unit operation and contamination scenario which can adversely impact the product and therefore the patient. A process exposure to external contamination is therefore a CCA.

During Part 2, the user should analyze each CCA in turn using the HACCP Tool - *Table C.*

HACCP Tool						
Process/Facility: *< insert process or facility >*				**Unit Operation:** *< insert name >*		
Hazard	**CCA**	**CCP (Y/N)**	**Critical Control Limit (CCL)**		**Hazard Identification**	**Control Mechanism**
			Measure	**Target**		
< insert a description of the contamination hazard >	< describe the critical control area(s) affected by this hazard >	< confirm whether this hazard is a critical control point or not >	< insert the measure and units >	< insert the target value >	< insert the control mechanism to be applied >	< insert description of how the control action will be applied >
			HACCP Summary			
< insert summary comments on the status of the HACCP and impact on outcome in terms of risk to the patient >						

Table D. HACCP Tool.[1]

HACCP Tool						
Process/Facility: Process ABC in Facility XYZ				**Unit Operation:** Crystallization – Seed Charging		
Hazard	**CCA**	**CCP (Y/N)**	**Critical Control Limit (CCL)**		**Hazard Identification**	**Control Mechanism**
			Measure	**Target**		
Normal shedding facility materials of construction above the open hand-hole falls into the crystallizer	Opening the hand-hole for 5 seconds	yes	Shedding materials in vicinity of hand-hole	Zero shedding materials above or around the hand-hole	The debris may be seen falling into the crystallizer however unlikely and so only noticed at the end of process	Temporary clean cover made of non-shedding materials to be placed around the hand-hole
Operator sheds contamination from hands as he opens the hand-hole and inserts the seed		yes		Zero shedding materials on operator hands	Debris is unlikely to be seen falling into the crystallizer and so only noticed at end of process	One use disposable gloves of a non-shedding material will be worn by operators for this operation
Operator sheds contamination from clothing as he opens the hand-hole and inserts the seed		yes		Zero shedding materials on operator clothing	The debris may be seen falling into the crystallizer however unlikely and so only noticed at end of process	One use disposable overalls made of a non-shedding material will be worn by operators for this operation
Contamination enters the seed from the dispensing room environment (Level III)	Dispensing seed in the Dispensing Room	yes	Level of clean in dispensing room	Zero cross contamination in dispensing room	Cross contamination will not be seen and so only noticed at end of process	The Level III area will be subject to a cleaning SOP. The dispensing room particulate count is controlled by normal processes
Contamination enters the seed from the equipment used to weigh the seed		yes	Level of clean of dispensing equipment	Zero cross contamination on dispensing equipment	Cross contamination will not be seen and so only noticed at end of process	One use disposable dispensing equipment to be used
Potential contamination from the equipment used to dispense the seed						
The control mechanisms in place as a part of the routine operation reduce the hazards to an acceptable level. All the control mechanisms will protect the unit operation and are all Level II solutions.						

Table E. Briefly Open (Exposed) HACCP Example.

- *Hazard* - it is usual to brainstorm the potential hazards which could occur within each CCA. In the case of reviewing a process exposure to external contamination, the hazards relate to the ways in which external contamination could enter the process.
- *CCA* - it is usual to collate together common hazards across a number of CCAs. For example, the dispensing of raw materials may impact a number of different reactor modules.
- *CCP (Y/N)* - by asking two key questions, the Critical Control Points (CCPs) can be defined for each potential hazard. A 'yes' (Y) or 'no' (N) should be inserted although for reviews, it would be usual to omit the non CCPs.
  - Question 1 – Does a control measure exist for this hazard within this unit operation?
  - Question 2 – Is control at this unit operation necessary to prevent, eliminate, or reduce the risk of the hazard to the product and therefore the patient?
- *Critical Control Limit (CCL)* - as previously defined, these are limits within which a hazardous situation needs to be controlled in order to safeguard product quality. For each CCL, there should be a defined measure with units and a target range, minimum and/or maximum.
- *Hazard identification* – the way that the normal operation of the process will highlight the hazard, should it occur, should be identified.
- *Control mechanism* – the way that the normal operation of the process will be used to bring the CCL back into the accepted range should be identified. This is the method by which the design will incorporate adherence to the CCL when the hazard occurs.
- *HACCP summary* - each time the HACCP is reviewed, the analysis and summary of the probable outcome for the process and product should be interpreted.

If the example scenario is used with Table D, then the following is the result. Table E highlights a number of hazards for this situation: when the contamination is likely to impact the process and therefore the product and ultimately the patient.

All the control limits proposed to mitigate the risks are to put protection in place during the dispensing and charging operation, in other words, give the situation Level II protection.

Risk versus Cost Benefits

The risk-based approach under discussion is an objective way to balance risk versus cost, i.e., risk to patient versus cost to manufacturer and ultimately the patient. It is appropriate to consider this balance. No process is 100 percent risk free – to be so would be cost prohibitive. However, risk to patient has to be appropriately managed and mitigated.

The tools in this White Paper are an attempt to stop manufacturers being too risk adverse and to using Level III – Controlled, as a solution to all product exposure scenarios. The cost of reactor modules, for example, can be significantly different and there should be a clear business rationale for this additional expenditure, i.e., to protect the patient.

Table F illustrates the relative differences in the cost of the different types of spaces.

It is important that manufacturers realize the significance of the decision to use the different levels of protection and to use data and objective reasoning to be risk appropriate.

Level of Protection	Level I	Level II	Level III
Relative Cost	1X	1.2X	!.7X

Table F. The relative differences in the cost of the different types of spaces (cost data courtesy of CE&IC API database) .

Conclusions and Recommendations

Different situations generate different data which require different analyses. The use of three different risk assessment techniques has demonstrated that they all developed the same outcome in terms of how the example risk scenario was mitigated. In terms of the Briefly Exposed (Briefly Open) concept, the tools demonstrate that time is not the only factor which determines risk level.

Manufacturers are encouraged to understand their process and to apply a method of risk assessment so that the concept of Briefly Exposed (Briefly Open) can be used to pragmatically design API facilities.

Future Steps

The results of this White Paper will be used in interactive sessions at various ISPE Conferences to generate further feedback on the concept of Briefly Exposed (Briefly Open). The overall goal is to give manufacturers a third option when considering levels of protection for their processes; to ensure that Level II – Protected is used appropriately to manage and mitigate risk to patient.

References

1. Melton, Trish "Real Project Planning: Developing a Project Delivery Strategy," Elsevier, Oxford, Great Britain (2008), ISBN: 978-0-7506-8472-9.

About the Authors

Stan Newberger, PE, is the co-founder and Principal of CE&IC. During his 37-year career, he has designed many pilot plants for the pharmaceutical and biotech industry. This has included the US's first fully validated bulk pharmaceutical chemical pilot plant for GlaxoSmithKline as well as pilot plants for Pfizer, Schering-Plough, Novartis, Boehringer Ingelheim, Bristol-Myers Squibb, Burroughs Wellcome, Hoffmann-La Roche, Wyeth, and others. Newberger also has designed bioprocess pilot plants for GlaxoSmithKline, Eli Lilly, Bristol-Myers Squibb, MedImmune, Laureate Pharma, and Emergent BioSolution. He holds a BS in chemical engineering from Brooklyn Polytechnic, an MBA from Rider College, and has taken further management courses at the Wharton School. He currently serves on the Advisory Board of Brooklyn Polytechnic University. As a member of ISPE, Newberger has given several courses on the design of pilot plants – both API and biotech industry. Newberger was the Technical Consultant for the United States Task Team for the development of the ISPE Baseline Guide: Active Pharmaceutical Ingredients (published in June 2007). He also has written the "*Concepts and Regulatory Philosophy,*" *Containment,*" and "*Pilot Plant*" Chapters in the ISPE Baseline® Guide on Active Pharmaceutical Ingredients. He can be contacted by telephone: +1-609-387-1700 or by email: snewberger@ceicinc.com.

CE&IC, 2 Terri Ln., Suite 125, Burlington, New Jersey 08016-4902, USA.

Dr. Trish Melton is Managing Director of MIME Solutions Ltd., an engineering and management consultancy providing project management, business change management, regulatory, and GMP consulting for pharmaceutical, chemical, and healthcare clients. Melton has worked as a project manager and project management consultant on engineering and non-engineering projects worldwide, predominantly within the global pharmaceutical industry. She is a chartered Chemical Engineer and a Fellow of the Institution of Chemical Engineers (IChemE), where she was the founder Chair of the IChemE Project Management Subject Group and recently authored an IChemE publication, the *Project Management Toolkit.* As an ISPE Member, Melton served on the working group that updated ISPE's *Bulk Pharmaceutical Chemicals Baseline® Guide*, and is the Founder Chair of the Project Management Community of Practice. She has presented on various subjects at ISPE conferences, including project management, quality risk management, and lean manufacturing. She also is the developer and main presenter on the ISPE Facility Project Management Course for those already working in pharmaceuticals and the associated Compliance Module intended for Project Managers entering the pharmaceutical industry. She can be contacted by telephone: +44-1829-75-9272 or by email: trish.melton@mimesolutions.com.

MIME Solutions Limited, Gable Cottage, Childwall Farm, Kelsall Road, Tarvin Chester, Cheshire, CH38NR, United Kingdom.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
November/December 2008, Vol. 28 No. 6

This article presents a performance verification study of a downflow booth via surrogate testing.

Performance Verification of a Downflow Booth via Surrogate Testing

by Hari Floura and John Kremer

Introduction

This article describes performance testing of a downflow booth in accordance with the ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment. The downflow booth was tested using lactose monohydrate in order to record the containment performance with respect to airborne particulate, when:

1. recommended operator work practices are followed
2. additional engineering controls are integrated within the downflow booth

For those not familiar with downflow booth technology, the downflow booth is an engineering control that achieves containment by air entrainment. A downflow booth achieves containment by providing unidirectional HEPA filtered airflow (Figure 1), typically 90 feet per minute when measured at approximately three feet (one meter) from diffuser screen, over the process zone. When the downflow booth is used as designed, this downward flow of unidirectional air entrains dust particulate released from the process, away from the operator. The particulate entrained in this downward flow of air is then recaptured by a low level exhaust and passed through pre-filters and HEPA filters to substantially remove the particulate. Typically this air is then re-circulated to the supply plenum resulting in a 'push/pull' system. Since the booth is an 'open front' design to allow easy access of materials and personnel, there is always a 'bleed in' of air that can potentially result in a positive pressurization of the system. To eliminate this situation, downflow booths are fitted with features to allow a 'bleed out' of air after the HEPA filter (positive pressure side of system) to maintain the design balance. This 'bleed out' of air, dependent on the application, is either re-filtered or released without further filtration. Due to the open nature of the downflow booths, they are very versatile and allow for a

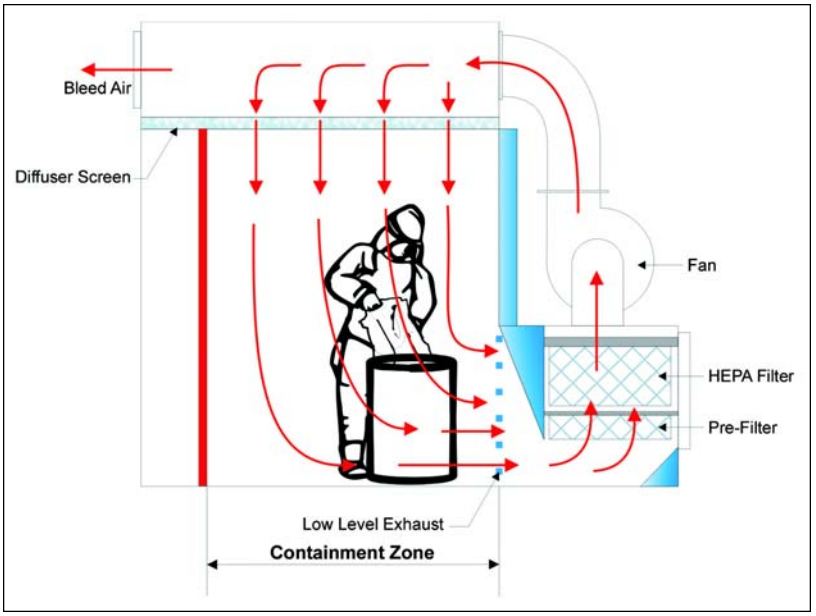


Figure 1. Unidirectional HEPA filtered airflow.

wide range of processes to be performed within them.

The downflow booth used for the performance testing was a standard re-circulating 2.0 meter wide booth. The booth's air processing system is comprised of two, rear mounted, bag-in/out filter banks arranged in parallel. Each bank consists of a high efficiency pre-filter and a HEPA filter. Polyester fabric (scrim) diffuser screens are used in the overhead supply plenum to ensure unidirectional downward airflow. Prior to surrogate testing, the downflow booth was tested to ensure it met performance specifications as defined by the downflow booth manufacturer. These tests were as follows:

- **Filter Penetration Test:** An aerosol challenge leak test was performed on each HEPA filter using a calibrated photometer and an aerosol generator that creates polydispersed particles predominantly 0.3 micron in size. The air flow through the filter was adjusted until the dP across the filter was 0.85 inches water gauge. (The differential pressure that would be seen across the filter when the downflow booth airflow is in normal running condition for new clean filter). The aerosol concentration injected upstream of the filter was 45 µg/l. The penetration of the aerosol was measured at 0.003% for the left HEPA (99.997% efficiency) and 0.002% for the right HEPA (99.998% efficiency). These measurements were within the required pass criteria for in place filter efficiency: >/= 99.97% at 0.3 micron level. Note the pre-filters were not in place during HEPA filter testing.

- **Supply Air Downflow Velocity and Uniformity**: The supply air velocity was measured with a rotating vane anemometer held three inches below the supply air scrim. Five points were measured in each of four scrim panels, for a total of 20 points. The average velocity for all 20 points was 100.5 ft/min. This met the pass criteria of average down flow velocity to be within 90 to 110 ft/min. The average velocity for each panel also was confirmed to be within 10% of the composite average down flow velocity. In addition, none of the individual points deviated more than 12% from the average velocity of the panel in which it was measured. These measurements met the specifications for the downflow booth. The total supply airflow was calculated and confirmed by measurement as 3360 cfm.

- **Bleed Air Volume:** In order to measure the bleed airflow from the downflow booth, a transition piece was placed over the bleed air outlet. It gradually channeled the air from the large rectangular bleed air diffuser into a 1 ft. square outlet, where the airflow was measured with a rotating vane anemometer. The measured bleed airflow was 430 cfm, equating to 11.4% of the total airflow (3360 cfm). This was within the required specification of five to 15% of the total airflow.

- **Return Air Flow Uniformity:** The return airflow was measured with a rotating vane anemometer held one inch away from the face of the grille. Four points were measured in each section of the return grille – left, center, and right – for a total of 12 points. The average velocity for each panel was within 10% of the composite average and none of the individual points deviated more than five percent from the average velocity of the panel in which it was measured. These measurements met the required pass criteria.

- **Smoke Tests:** Smoke tests were performed to demonstrate the airflow characteristics of the booth. The tests were video taped for record. The tests showed that:

  - The containment boundary or safe work zone extended 52" forward from the rear wall of the booth.
  - Within the safe work zone, the air flowed uniformly from the air supply scrim in the booth ceiling down to the return air grille in the rear wall of the booth.
  - The air moved in "plug flow" fashion, without back-mixing or diffusion.
  - Disturbances in the air stream caused by obstacles in the booth (equipment, people, etc.) were quickly resolved and did not cause air to flow back up into the operator's breathing zone.

The results of this performance verification testing demonstrated that the 2.0 meter wide downflow booth was operating within the defined performance criteria.

Surrogate Testing Protocol

The task to be performed in the booth was designated as drum-to-drum transfer of 25 kg of Lactose. This task was selected based on the following criteria:

- Drum-to-drum transfers by hand scooping or direct discharge from a drum liner are common tasks that are performed at the majority of pharmaceutical facilities.
- It is an 'open' and manual process, reliant on operator technique, so it would challenge the equipment to a reasonable level and provide suitable parallel for 'real world' tasks.
- The equipment and materials required to perform the task are readily available.
- Lactose is the recommended surrogate of the ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment, (Appendix G) and is readily available. The surrogate material was sourced to be in compliance with the Good Practice Guide. [Lactose-313, NF Monohydrate; Product No. 661550, Batch 8506060313]. The Lactose used had a particle size distribution of 75% (by weight) less than 37 micrometers with 24% between 75 and 37 micrometers, and one percent larger than 75 micrometers. Although not a crystalline material, lactose has physical characteristics, such as particle size and dustiness, similar to the products typically handled in a pharmaceutical environment. Additionally, it is detectable at very low concentrations in air.

Due to the space limitations within the booth, the testing protocol was developed for one operator to perform out all of the required tasks. To reduce the risk of potentially contaminating the test area and thereby raising the background levels, we arranged the tasks from those expected to release the least amount of contamination to those expected to release the most, as follows:

1. Downflow Booth with Additional Controls:

The manual transfer of lactose (25 kg) from the bulk drum to one receiving drum (in all instances the drums to be fitted with double liners) within the downflow booth with the addition of a ventilated charging collar to improve dust containment and a drum handler to improve ergonomics. Note that the ventilated charging collar provides additional control only via additional containment by air entrainment and this is still considered an open process.

1.1 Transfer the drums (bulk product and receiving) into the downflow booth.
1.2 Stage the bulk drum on the drum handler and the receiving drum in front of it. De-lid the drums.
1.3 Locate the ventilated collar on to the opening of the receiving drum and stage the liners. The operator should use the drum handler to position the opening of the bulk drum as close as possible to the receiving drum. The operator shall use the drum handler to angle the bulk drum to allow direct liner to liner transfer by pouring/scooping to the receiving drum. The operator also shall ensure that the opening of the liner containing the bulk lactose is kept below the extraction slots of the ventilation collar during liner opening and material transfer.
1.4 The bulk drum liner is verified empty by slowly pulling it out of the bulk drum over the top of the ventilated collar; being careful to ensure that the liner opening remains below the extraction slots. Residual material encountered during this process is worked free and transferred into the receiving drum. Once empty, the bulk liner is carefully balled up (within the collar) and passed into a sleeved trash chute that is incorporated into the ventilated collar.
1.5 Tie off the liners for the receiving container and re-lid the drum. Remove one layer of gloves and place into bulk receiving drum and re-lid the bulk drum.

2. Downflow Booth with No Additional Controls:

The manual transfer of lactose (25 kg) from the bulk drum to one receiving drum (in all instances the drums to be fitted with double liners) within the downflow booth with no additional controls or ergonomic aids.

2.1 Transfer the drums (bulk product and receiving) into the downflow booth.
2.2 Stage the drums to the rear of the booth and de-lid drums and stage liners. The operator should hand scoop the lactose until sufficient material is transferred to allow the liner containing the remaining material to be lifted out of the drum to allow direct discharge from the liner by pouring into the receiving drum.
2.3 When liner is empty, place it back into the now empty bulk product drum. Tie off the liners for the receiving container and re-lid the drum. Remove one layer of gloves and place into bulk receiving drum and re-lid the bulk drum.

3. Downflow Booth Ventilation System Disabled:

The same procedure as described in item two (downflow booth). The purpose for this test would be to establish the magnitude of airborne dust levels for a drum to drum transfer if no engineering controls were employed. This data was considered useful as it would allow us to ascertain the amount of protection provided by the downflow booth technology

As per the recommendations of the ISPE Good Practice Guide (Section 4.5 Clothing), the clothing for the operator was as follows:

3.1 Tyvek® one-piece disposable suit
3.2 Several layers of impermeable gloves, a layer of gloves is to be removed after each task is completed and discarded. A layer of gloves also should be removed after conducting a task that results in a high level of dust on the gloves.

The hairnet/cover was excluded as there were no cGMP requirements since the testing was performed in a non-GMP area.

An operator was selected and trained on the simulation. Attention to good work practices to reduce airborne particulate generation was stressed. As a result of the training it was determined that each task required an average duration of 20 minutes, when performed following the operator procedures as outlined previously. Based on this data and to ensure that the testing yielded a relevant number of samples, each task would be repeated a total of three times. To further ensure that a sample representative of all the dust emitted from the task was collected, the sampling was extended for an additional 15 minutes at the end of each iteration with the operator remaining in the booth for that period (as recommended by the ISPE Good Practice Guide – 'Equipment Specific Test Protocols,' page 32). As per the protocol, following the completion of the task and extended sampling period, all air sampling pumps were stopped and the filter cassettes removed and changed before proceeding with the subsequent process iteration.

Since very high concentrations of airborne lactose were expected during the test with the downflow booth disabled, there was concern that this task would contaminate the downflow booth and testing area to a point that the raised background levels would affect any future testing. For this reason, only a single iteration of this test was performed. Also, the 15 minute sample extension period was reduced to five minutes. Given the high airborne concentrations ex-

pected, it was felt that the shortened duration of the extension period would have no significant impact on reported airborne concentration obtained by these samples.

Air Sampling Method

Operator Breathing Zone (OBZ) air samples were collected during this study to quantify the typical exposures for the operator while performing the designated tasks. The operator wore a calibrated air monitoring pump attached to his belt and a sample collection device (25 mm, 1.0 µm PTFE filter in two-piece blank, conductive cassette) attached to his collar. The filter cassette was attached to the pump with Tygon® tubing.

Area air samples also were collected in fixed locations inside and outside of the downflow booth - *Figure 2*. This included three area air samples inside the booth and just outside the "safe working zone." Three area air samples also were collected outside the booth in order to assess the potential for particulate migration out of the booth during the surrogate operation. All the area air samplers were oriented to face into the downflow booth The sample locations were in accordance with the recommendations of ISPE Good Practice Guide, 'Equipment Specific Test Protocols', (page 34) and were as follows:

- Inside booth: eight inches off left side wall and eight inches outside safe work zone
- Inside booth: in the center of the booth and eight inches outside safe work zone
- Inside booth: eight inches off right side wall and eight inches outside safe work zone
- Outside booth: eight inches outside booth in front of left side wall
- Outside booth: five feet outside and in the center of the booth
- Outside booth: eight inches outside booth in front of right side wall

Planning and careful field techniques were required when air sampling to ensure that meaningful data was collected and that the samples are not cross-contaminated during collection, resulting in false positives. With this in mind, the following field techniques were employed:

- Pre- and post- monitoring verification of sample pump's airflow calibration. This is done by a comparison to a secondary, NIST traceable, calibrated standard for three trials, that were then averaged.
- The lower of the pre- or post- monitoring calibration averages were used to calculate the sample volume for a given pump.
- Careful observation and recording of sample pump run times in order to determine an accurate total sample volume.
- Over-handling of filters was avoided as much as possible.
- Filters were always handled with clean powder-free gloves.
- Filters were stored in sealed plastic "zip-lock" bags with separate bags for clean and used filters. If the filter cassettes were seen to be dusty (pump casing was examined for evidence), the cassettes were wiped off after capping before placing the used filters into the plastic bag.
- Filter cassette tips were stored in separate clean plastic "zip-lock" bag during air monitoring. The colors were reversed on used filters (red tip on inlet) to distinguish from clean filters (blue tip on inlet). Touching of the filter cassette inlet opening and the filter cassette tip pointed ends were avoided as much as possible.
- Tips were placed on filters after turning pumps off.

As previously stated, the air sampling was extended by 15 minutes at the end of each task iteration with the operator remaining in the booth for that period. At the end of this 15 minute 'rest period,' all air sampling pumps were stopped and the filter cassettes removed and changed before proceeding with the subsequent process iteration.

Background area air samples also were collected prior to conducting any work to determine if the surrogate material was detectable in workplace air, either from pre-existing operations or other sources of contamination, such as preparation for this testing.

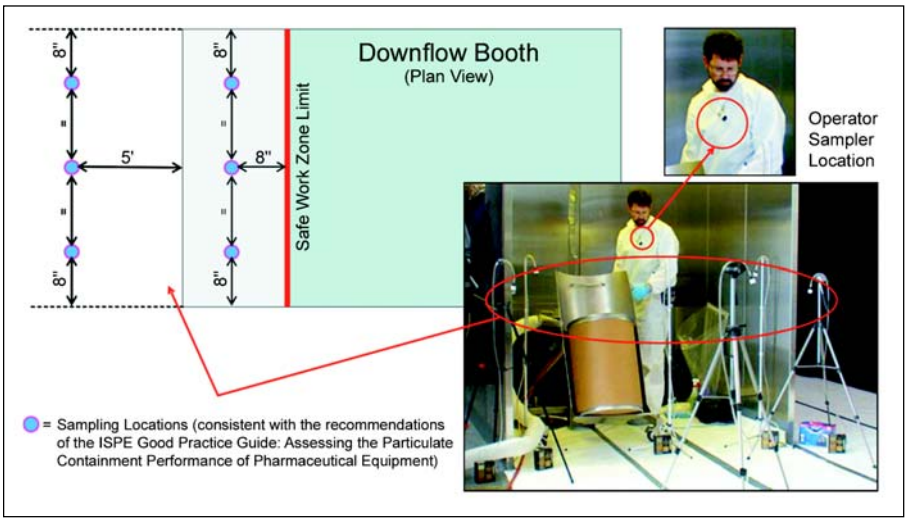


Figure 2. Downflow booth (plan view).

Test Equipment

The test equipment used was as follows:

- Air Monitoring Pumps were operated at a flow rate of approximately 2.0 liters per minute. These pumps were calibrated before and after sampling by an airflow meter calibrated to the National Bureau of Standards (NBS).
- Sample collection device (25 mm, 1.0 µm PTFE filter in two-piece blank, conductive cassette).

Analysis

All air samples were submitted to an

independent laboratory for sample analysis for lactose. Each sample was identified using a unique number and stored and shipped the samples in refrigerated containers to minimize the potential for sample degradation. The field blanks were handled in the same manner as the other air samples, except that no air was drawn through the filter cassettes.

The samples were analyzed using High Performance Liquid Chromatography (HPLC) with Pulsed Amperometric Detection (PAD). The sample was extracted from each PTFE filter using in situ methodology with a suitable solvent for lactose. The analytical reporting limit for lactose using this method is two nanograms per air sampling filter.

It also should be noted that the test results were not time weighted and reflect the actual average concentration over the sample time.

Background Testing

Two days were taken to complete the testing and prior to beginning work on each day of this performance verification study, two background area air samples were collected in the testing area both inside and outside the booth in locations that would subsequently be used for the static area air samples. The results of these samples were as follows:

Background Area Air Samples Collected on Day One

- Inside: <0.01 µg/m^3
- Outside: <0.01 µg/m^3

Background Area Air Samples Collected on Day Two

- Inside: 0.05 µg/m^3 (Elevated reading, assumed to be due to moving of potentially contaminated bulk containers into the downflow booth prior to background sampling on day two.)
- Outside: <0.01 µg/m^3

Additionally, one field blank was submitted for analysis for approximately every 10 air samples collected. Since a total of 53 air samples were collected in this study, five field blanks were submitted for analysis. The results of these field blank samples were all reported as less then <2ng per filter.

Observations During Testing of Booth with Additional Controls

The first test required that the downflow booth be tested with a ventilation sleeve containment system and drum handler as an additional engineering control - *Figure 3*. This system was selected as it has the following features:

- Provides high-velocity ventilation 360 degrees (425 cfm) around the perimeter of the localized working area, creating a cross-sectional plane of exhaust. Exhaust HEPA filter prior to discharge.
- Integrated bag out port
- Integrated drum handler to improve ergonomics

The ventilation sleeve containment system was connected to a stand alone Air Handling Unit (AHU) fitted with a HEPA

Figure 3. Ventilation sleeve containment system and drum handler.

filter in order to generate the required airflow (425 cfm). This stand alone AHU was located outside the downflow booth. It should be noted that the downflow booth was not rebalanced at this stage to assess the effect of the additional 425 cfm of air exhausted by the ventilation sleeve out of the booth. Differential pressure measurements across the polyester air diffusers did not appreciable change when the collar was in use, indicating that the additional 425 cfm make up air most likely entered the booth through the booth's open front. A localized disruption of the typical unidirectional airflow within the booth can be expected adjacent to the ventilated collar. The collar exhaust flow rate was monitored for the duration of the testing and was held constant.

In order to achieve the transfer, the open end of the liner containing the lactose was extended through the opening of the ventilated collar and into the receiving drum. The lactose was then transferred from the bulk drum by 'massaging' the contents slowly through the liner into the receiving drum - *Figure 4*. As soon as the liner was nearly empty, it was removed from the bulk container by the operator and carefully inverted to fully discharge the contents into the receiving container, all the time ensuring that the open discharge side liner was never raised above the high velocity exhaust slot of the ventilated collar. Once empty, the liner was disposed of by posting it into the sleeved waste port on the ventilated collar (located below the velocity exhaust slot of the ventilated collar). The ventilated collar was then lifted off of the receiving container and placed on the floor of the downflow booth. The liner containing the lactose in the receiving drum was then tied off and the drum re-lidded.

Figure 4. Lactose transfer from bulk drum by 'massaging' the contents slowly through the liner into the receiving drum.

The waste out bag containing the waste liner and all used gloves were placed within the bulk drum and sealed re-lidding it.

It also was recorded that due to space limitations in the booth created by the drum handler, in order to remove the empty bulk drum and to replace it with a new one an individual outside of the booth was needed. The bulk drum containing the waste was first transferred to this individual and then the new receiving drum with liners was transferred to the operator, at the safe work line. This task was accomplished as carefully as possible to not disturb or unintentionally contaminate the static area air samplers

Results for Booth with Additional Controls

A total of 21 air samples were collected for all the task iterations using this configuration as follows:

- Operator Breathing Zone Air Samples: The exposure of one operator was assessed for three iterations (three samples) of the transfer process; each iteration took between 32 and 35 minutes to complete (including the 15-minute extension period)

  Results Range: <0.03 to 0.04 µg/m^3
  Mean: 0.03 µg/m^3

- Area Air Samples: A total of 18 area air samples were collected at three locations within and three locations outside the downflow booth.

  Results Inside - Range: <0.03 to <0.03 TR* µg/m^3
  Inside - Mean: 0.03 µg/m^3
  Outside - Range: <0.03 to 0.05 µg/m^3
  Outside - Mean: 0.03 µg/m^3

**TR = Trace amount detected on sample. A trace amount indicates an analytical peak that shows the presence of lactose on the sample, but at a level below the reporting limit for the air volume collected. It is used to indicate that the results show that lactose was present on the sample, but an amount below the two nanogram lower limit of quantification.*

Observations during Testing of Booth without Additional Controls

For the second test, the only engineering control used was the downflow booth. As per the recommendations for operating in a downflow booth, the operator positioned the drums as close as possible to the low level exhaust located at the back of the booth. The bulk drum also was placed as close as possible to the receiving container to minimize the distance required to scoop the lactose. The operator then carefully transferred by hand scooping the lactose from the bulk drum to the receiving drum, at times ensuring that the scoop was placed entirely inside the receiving container before dispensing the contents - *Figure 5*.

As soon as the liner was nearly empty, it was removed from the bulk container by the operator and carefully inverted to fully discharge the contents into the receiving container. The receiving liner was then tied off and the drum re-lidded. The waste liner and all used gloves were placed into the bulk drum and sealed by re-lidding it.

Results for Booth without Additional Controls

A total of 21 air samples were collected for the drum to drum transfer of lactose using the downflow booth as the only engineering control as follows:

- Operator Breathing Zone Air Samples: The exposure of one operator was assessed for three iterations (three samples) of the transfer process; each iteration took between 37 and 39 minutes to complete (including the 15-minute extension period)

  Range 0.64 to 1.54 µg/m^3
  Mean: 1.01 µg/m^3

- Area Air Samples: A total of 18 area air samples were

Figure 5. An operator carefully transfers; by hand scooping the lactose from the bulk drum, to the receiving drum, ensuring the scoop is placed entirely inside the receiving container before dispensing the contents.

collected at three locations within and three locations outside the downflow booth.

Range Inside - Range: <0.02* to 0.06 µg/m³
Inside - Mean: 0.03 µg/m³
Outside - Range: <0.02 to 0.05 µg/m³
Outside - Mean: 0.02 µg/m³

** Note that due to the variation of total sampled air volumes (a function of both sample rate and sample time), a lower reportable airborne concentration of 0.02 µg/m³ was achievable for this test as compared to the 0.03 µg/m³ limit indicated in the result of the booth with additional controls*

Observations during Testing of Booth with Ventilation Disabled

For the third and final test, the downflow booth air handling system was disabled. The tasks performed by the operator were exactly the same as those conducted for the test two with the downflow booth operating, except that the operator was slightly quicker in completing the product transfer. As previously stated since there was a concern with lactose contamination of the booth and the testing area, only one iteration of this test was performed and the 15 minute extension of the sampling period used in the previous tests was shortened to five minutes.

Results of Booth with Ventilation Disabled

Total of seven air samples were collected for this test:

- Operator Breathing Zone Air Sample: The exposure of one operator was assessed for a single iteration (one sample) of the transfer process; the iteration took 24 minutes to complete (including a 5-minute extension period)

  Results 2,250 µg/m³

- Area Air Samples: A total of six area air samples were collected at three locations within and three locations outside the downflow booth.

  Results Inside - Range: 51.6 to 177.0 µg/m³
  Inside - Mean: 123.5 µg/m³
  Outside - Range: 10.0 to 32.3 µg/m³
  Outside - Mean: 20.0 µg/m³

Conclusion

Historical data shows that downflow booths typically control operator exposures to between 100 and 50 µg/m³ based on eight-hour time weighted averages. The results of this study indicate that even greater control is possible when good operating procedures and transfer technique are rigidly followed by an operator.[3,4,5,6] The results (Tables A, B, and C) show that downflow booth technology is highly effective in reducing and controlling high levels of airborne lactose dust and the potential exposure to the operator when procedures and techniques are applied precisely. The results show that when coupled with good technique, the downflow booth provided exposure control to 1 µg/m³ for lactose for the period of

	Booth with Additional Controls	Booth with No Additional Controls	Booth with Ventilation Disabled
Operator Breathing Zone Range	< 0.03 to 0.04 µg/m³	0.64 to 1.54 µg/m³	2,250 µg/m³
Operator Breathing Zone Mean	0.03 µg/m³	Mean: 1.01 µg/m³	Only one sample collected
Area Air Samples Inside Range	< 0.03 to < 0.03 µg/m³	< 0.02 to 0.06 µg/m³	51.6 to 177.0 µg/m³
Area Air Samples Inside Mean	0.03 µg/m³	0.03 µg/m³	123.5 µg/m³
Area Air Samples Outside Range	< 0.02 to 0.05 µg/m³	< 0.02 to 0.05 µg/m³	10.0 to 32.3 µg/m³
Area Air Samples Outside Mean	0.03 µg/m³	0.02 µg/m³	20.0 µg/m³

Table A. Showing summary of results.

Date	Sample #	Type of Sample	Activity	Time(min)	Air Volume (L)	Conc. ($\mu g/m^3$)
8/25/06	082506-01	Background	Background area air sample (inside)	76	167.6	0.05
8/25/06	082506-02	Background	Background area air sample (outside)	76	167.6	< 0.01
8/25/06	082506-03	OBZ	Drum-to-drum transfer of 25 Kg lactose by hand scooping (iteration #1)	37	83.1	1.54
8/25/06	082506-04	Area (in)	Static area air sample inside booth; LEFT side (iteration #1)	37	80.5	< 0.02
8/25/06	082506-05	Area (in)	Static area air sample inside booth; CENTER (iteration #1)	37	81.6	< 0.02
8/25/06	082506-06	Area (in)	Static area air sample inside booth; RIGHT side (iteration #1)	37	79.6	< 0.03
8/25/06	082506-07	Area (out)	Static area air sample outside booth; LEFT side (iteration #1)	37	80.8	< 0.02TR
8/25/06	082506-08	Area (out)	Static area air sample outside booth; CENTER (iteration #1)	37	81.6	< 0.02
8/25/06	082506-09	Area (out)	Static area air sample outside booth; RIGHT side (iteration #1)	37	83.3	< 0.02
8/25/06	082506-10	Field Blank #1	N/A	N/A	N/A	< 2 ng
8/25/06	082506-11	OBZ	Drum-to-drum transfer of 25 Kg lactose by hand scooping (iteration #2)	37	83.1	0.64
8/25/06	082506-12	Area (in)	Static area air sample inside booth; LEFT side (iteration #2)	37	80.5	0.06
8/25/06	082506-13	Area (in)	Static area air sample inside booth; CENTER (iteration #2)	37	81.6	< 0.02
8/25/06	082506-14	Area (in)	Static area air sample inside booth; RIGHT side (iteration #2)	37	79.6	< 0.03
8/25/06	082506-15	Area (out)	Static area air sample outside booth; LEFT side (iteration #2)	37	80.8	< 0.02TR
8/25/06	082506-16	Area (out)	Static area air sample outside booth; CENTER (iteration #2)	37	81.6	< 0.02
8/25/06	082506-17	Area (out)	Static area air sample outside booth; RIGHT side (iteration #2)	37	83.3	< 0.02
8/25/06	082506-18	OBZ	Drum-to-drum transfer of 25 Kg lactose by hand scooping (iteration #3)	39	87.6	0.86
8/25/06	082506-19	Area (in)	Static area air sample inside booth; LEFT side (iteration #3)	39	84.8	< 0.02
8/25/06	082506-20	Area (in)	Static area air sample inside booth; CENTER (iteration #3)	39	86.0	< 0.02
8/25/06	082506-21	Area (in)	Static area air sample inside booth; RIGHT side (iteration #3)	39	83.9	0.03
8/25/06	082506-22	Area (out)	Static area air sample outside booth; LEFT side (iteration #3)	39	85.2	< 0.02TR
8/25/06	082506-23	Area (out)	Static area air sample outside booth; CENTER (iteration #3)	39	86.0	0.05
8/25/06	082506-24	Area (out)	Static area air sample outside booth; RIGHT side (iteration #3)	39	87.8	< 0.02
8/25/06	082506-25	Field Blank #2	N/A	N/A	N/A	< 2 ng

Table B. Results of lactose surrogate air sampling downflow booth (only).

operation.

Further, the combination of a ventilated collar and drum handler with the downflow booth successfully demonstrated exposure control well below 1 µg/m^3 for lactose for the period of operation. There was only one detectable reading from the sample taken in the operator's breathing zone (0.04 µg/m^3) and one detectable reading among all the static area air samples collected (0.05 µg/m^3).

The case for the use of engineering controls such as the downflow booth for open transfer operations also was confirmed by the high levels of lactose dust measured when no engineering controls are employed (2,250 µg/m^3). This information is of further value as it gives a reasonable indication of the protection factor (the ratio of observed concentration without protection to that when protective measures are used) that can be provided by the use of downflow booth type technology; in excess of 2000.

The data collected also provides good evidence that the air sampling results in this study were not adulterated by background levels of lactose or from any other source. Three of the four results collected for the four background area air samples submitted for analysis were below the analytical reporting limit for the sample collection period (greater than 60 minutes). The one detectable reading on Day 2 was likely due to moving of bulk containers into the downflow booth, which occurred after the air samplers were started. In addition, the five field blanks showed no reportable levels of lactose.

As previously stated, throughout the study the operator always removed his outer gloves after handling the receiving container and wiped down the downflow booth's exhaust

Date	Sample #	Type of Sample	Activity	Time(min)	Air Volume (L)	Conc. ($\mu g/m^3$)
8/25/06	082506-26	OBZ	Drum-to-drum transfer of 25 Kg lactose by hand scooping (w/out vent.)	24	53.9	2250.0
8/25/06	082506-27	Area (in)	Static area air sample inside booth; LEFT side (iteration #1)	24	52.2	142.0
8/25/06	082506-28	Area (in)	Static area air sample inside booth; CENTER (iteration #1)	24	52.9	177.0
8/25/06	082506-29	Area (in)	Static area air sample inside booth; RIGHT side (iteration #1)	24	51.6	51.6
8/25/06	082506-30	Area (out)	Static area air sample outside booth; LEFT side (iteration #1)	24	52.4	17.6
8/25/06	082506-31	Area (out)	Static area air sample outside booth; CENTER (iteration #1)	24	52.9	10.0
8/25/06	082506-32	Area (out)	Static area air sample outside booth; RIGHT side (iteration #1)	24	54.0	32.3
8/25/06	082506-33	Field Blank #3	N/A	N/A	N/A	< 2 ng

Table C. Results of lactose surrogate air sampling downflow booth (without ventilation).

plenum where a distinct ring of particulate contamination was noted. When the additional engineering controls were utilized, the operator ensured that his technique did not allow the material being transferred to leave the local exhaust ventilation zone during the transfer process, and the operator removed his outer gloves after handing the receiving container and wiped down the drum lift after each iteration.

However, we also must state that these results are specifically for airborne lactose and while they provide a valuable benchmark, actual containment characteristics for alternate compounds can only be known by testing with those compounds. Additionally, in the process environment where the pace of work is accelerated and operators may not always use good technique, the exposure levels experienced by the operator are likely to be higher, perhaps by as much as an order of magnitude dependent on the material being handled and the process operation.

Based on the results of this study, we can conclude:

- The performance of a downflow booth can be significantly enhanced by the use of a double lined drum and a ventilated collar integrated with a drum handler to improve ergonomics.
- Operator technique and strict adherence to procedures can significantly improve the performance of a downflow booth with no additional controls.
- Similar results may be achieved and repeated by a well trained and conscientious operator, rigidly following recommended procedures in combination with a downflow booth.

References

1. *ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment*, International Society for Pharmaceutical Engineering (ISPE), First Edition, January 2005, www.ispe.org.
2. McCarthy, M.S., CIH CSP, Performance Verification of AEC Downflow Booth via Surrogate Air Monitoring with Lactose Monohydrate, October 24, 2006.
3. Downflow booth performance data collected by Hari Floura from various client confidential projects.
4. Proulx, D., Eherts, D., "What a Pharmaceutical Company looks for from an Outsourced Potent API/Formulate, Fill and Finish Contractor," presented at the ISPE *Potent Compounds Containment Conference*, 2002.
5. Richards, P., "Containment Systems Designs to Handle Potent Compounds in an API Pilot Plant," presented at the ISPE *Potent Compounds Containment Conference*, 2002
6. Floura, H., "Downflow Dust Control Booth, Performance Testing of three configurations of 2.0m Dispensing Booth with reference to Operator Protection and Dust Containment," data collected while employed by Extract Technology Ltd., report by Vale Services.

Acknowledgements

Mark S. McCarthy and John Ferris of SafeBridge Consultants, Inc® for all their help and insight during the testing and the preparation of this article. SafeBridge Consultants, Inc® conducted the performance verification testing in order to ensure impartiality with respect to the results collected from this exercise.

Katherine Din Floura (Floura LLC), Marc Greenleaf (AEC), Mark S. McCarthy, and Ann Williams (AEC) for their assistance in proof reading and editing this document.

Thanks to EHS Solutions for the use of their ventilated charging collar in this performance verification.

About the Authors

Hari Floura is the President of Floura LLC. Since obtaining his degree in industrial design engineering BA (Hons) in 1988, Floura has worked exclusively in the field of containment technology within the pharmaceutical industry. During this time, Floura has held positions with Extract Technology Ltd., Process Containment Technologies Ltd., Total Process Containment Ltd., Kvaerner Inc., Parsons Inc., in addition to establishing and managing the USA offices of Applied Containment Engineering (ACE), in the position of President of Operations. Floura was a pioneer in introducing the concepts of ergonomics and ergonomic modeling to the industry along with developing many of the design concepts used in containment equipment today. In addition, he has provided consultancy to many major pharmaceutical companies with respect to their containment guidelines, facility and containment system designs. He also is a member of and regular presenter for ISPE and contributed to the ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment. He can be contacted by telephone: +1-609-259-7136 or by email: hari@flourallc.com.

Floura LLC, 21 Prestile Place, Robbinsville, New Jersey 08691, USA.

John Kremer has more than 20 years of experience in the design, manufacturing, and application of engineered controls within hazardous work environments. He is currently Vice President of Engineering with Applied Engineering Controls (AEC); serving the pharmaceutical, nuclear, and industrial markets. AEC is a supplier of standard and customized air filtration systems, down flow booths, ventilated work stations, localized extraction systems, radiation shielding, and other specialized containments. He holds degrees in structural engineering and physics from Clarkson University, and is an active ISPE, IEST, and ANS member. He can be contacted by telephone: +1-860-445-0334 or by email at: jkremer@rpsct.com.

Applied Engineering Controls, 60 Leonard Dr., Groton, Connecticut 06340, USA.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
November/December 2008, Vol. 28 No. 6

Shanghai Support for ISPE China Members

To better support its Chinese Members, and to more effec tively bring education and training to the burgeoning pharmaceutical industry in Asia, ISPE has opened an office in Shanghai, China.

Moving into 2009, pharmaceutical companies will increasingly rely on China for integrated research, development, and innovative manufacturing solutions. The Chinese pharmaceutical industry is 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. Because of China's increasing role on the world stage, and ISPE's growing involvement with activities in China, the Society found it imperative to support its initiatives with help from local ISPE staff.

For example, the China Center for Pharmaceutical International Exchange (CCPIE) invited ISPE to collaborate with them in bringing an exceptional learning opportunity to Chinese pharmaceutical professionals. The ISPE China Conference was held 11-12 November 2008 in conjunction with the 13th China International Pharmaceutical Industry Exhibition at the China International Exhibition Center in Beijing. (The CCPIE acts as the conduit between professional organizations and the SFDA, China's pharmaceutical regulatory agency. The collaboration between ISPE and CCPIE is as pivotal as it is historic, as the CCPIE also trains members of the SFDA.)

ISPE President and CEO Bob Best during a recent visit to the Shanghai office.

In addition, the Society recently announced that Sichuan University is forming ISPE's first Student Chapter in China with more than 100 Student Members.

You can reach ISPE's China office at:

Suite 2302, Wise Logic International Centre
66 North Shan Xi Road, Shanghai 200041, China
Tel: +86 21-5116-0265, Fax: +86 21-5116-0260
Email: china@ispe.org, http://www.ISPE.org.cn/

Introducing the 2008-2009 ISPE Board of Directors

Officers

Each to serve the Society for a term beginning 28 October 2008.

Chairman

Charles P. Hoiberg, Executive Director, Pfizer Global Regulatory CMC Group

Vice Chairman

Alan Mac Neice, Senior Director for Projects, Elan Biologics division

Treasurer

Andre Walker, Director of Manufacturing Engineering and Facilities, Biogen Idec

Secretary

Dr. Arthur (Randy) Perez, Executive Expert, IT Quality Assurance, Novartis Pharmaceuticals

New Directors

Each to serve the Society for a two-year term beginning 28 October 2008.

Joan Gore, Manager, Clinical Trial Packaging and Support Services, Eli Lilly and Co.

Tomiyasu Hirachi, Representative Director and President, EEM Japan Co., Ltd.

Stephen Tyler, Director of Strategic Quality and Technical Operations, Abbott Laboratories

Dr. Guy Wingate, Quality Director, GlaxoSmithKline

Directors in Place

The following Directors were elected in 2007 to serve a two-year term.

Nuala Calnan, Principal Consultant, PM Group

Charlotte Enghave, PhD, Senior Consultant, NNE Pharmaplan

Nigel Frost, Managing Director, Thermal Transfer Ltd.

Damian J. Greene, Director/Team Leader, Pfizer Inc.

David E. Petko, PE, Senior Director, Auxilium Pharmaceuticals, Inc.

Stephanie A. Wilkins, PE, President, PharmaConsult US Inc.

Past Chairman

The Past Chairman automatically serves one additional year on the Board.

Bruce S. Davis, Global Capital Director, AstraZeneca

ISPE Barcelona Conference to Focus on Applying Science and Risk-Based Approaches

The ISPE Conference on Applying Science and Risk-Based Approaches to be held 1 – 4 December in Barcelona, Spain, will feature the following sessions:

Successful Management of Sterile Products Quality

This seminar will provide the latest information in the sterile manufacturing arena on best practices used to manage quality of product for patient safety. An update on current European and FDA Good Manufacturing Practice (GMP) Regulations will be given with discussion on the implementation of Annex 1 and ISO guidelines in the area of healthcare products. Speakers will address risk assessment issues, best practices for new regulation and technology, regulatory updates, project facility issues associated with refurbishment, new technologies, and barrier systems. The updated ISPE Baseline® Guide for Sterile Products and Processes also will be discussed. Speakers include regulators from the FDA and MHRA, plus industry leaders and professionals active in handling sterile products.

Applied Risk Management – Addressing Cross Industry Challenges

This seminar will introduce general principles of risk management which are applicable across the industry and aims to be a practical workshop introducing different risk types and challenges, including quality (ICH Q9); project (cost, time and scope risks); operational (risks associated with health and safety, containment, maintenance, and quality); and business (supply chain, commercial, and competitive risks). Speakers include leaders in the field of risk management and subject matter experts from ISPE Communities of Practice (COPs). During interactive sessions, speakers will present concepts, tools and case studies, and offer hands-on practice in applying these.

Achieving Operational Excellence in Biomanufacturing: Trends and Case Studies

This seminar will consider how to achieve operational effectiveness and will consider key issues such as the impact of disposable technology, flexible operation, fast turnaround, and cost implications. Practical techniques such as high titer cell culture, bio separation, DSP, continuous chromatography, and aseptic fill and finish will be discussed alongside the strategic, operational, and economic issues involved in their use. With sessions on waste management and treatment, facilities, lean design, and the global hot topic – sustainability – the seminar speakers include technical experts and leaders in biomanufacturing innovations.

Containment Technology Forum – Applying ICH Q9 Principles to Selecting

Increasing containment is necessary to minimize contamination of the operator environment and avoid cross-contamination from one product to the other. Each situation needs to be evaluated on a case-by-case basis, using risk assessment tools such as ICH Q9 and ISPE's Risk-MaPP Baseline® Guide to identify the appropriate risk controls, as well as set health-based limits to address both cross-contamination and operator protection. To select appropriate containment technology, a partnership of healthcare professionals with focus on identification of hazards, exposure assessments, risk evaluation, and implementation of risk controls – as well as considering the economic and regulatory impact of non-compliance – and engineers has to be implemented.

Validation of Process Control Systems (VPCS) – A Major Revision of the GAMP® Good Practice Guide

This seminar is intended to provide delegates with the latest principles, concepts, and approaches to the validation of process control systems. The seminar will provide details on how the planned revision to the GAMP Good Practice Guide for the Validation of Process Control Systems will incorporate the principles in the recently published GAMP 5 Guide and harmonize with other related Good Practice Guides.

Using a lifecycle approach to VPCS risk management issues, speakers will identify core issues, including project management, governance procedures, operational approaches, and supplier assessment.

Lyophilization: Scientific Issues to the Process and Introduction to Risk-Based Approach

Using a series of workshops and case studies, this seminar covers the key issues involved in applying a risk-based approach to lyophilization. Covering theory and practice, sessions will combine specific aspects of risk assessment, identification of new technologies and techniques (including sterilization methodologies, the development of PAT tools, and new control methods), and trends in monitoring. Taking a pragmatic approach to the problems of this complicated practice, speakers from a range of backgrounds and approaches – industry, suppliers, and manufacturers – take a lifecycle approach to addressing some of the challenges and risks. Regulatory expectations, including the application of GMP Annex 1 are covered.

Martin and Perez Win 2008 Article of the Year Award

Pharmaceutical Engineering is pleased to congratulate **Kevin C. Martin and Dr. Arthur (Randy) Perez**, authors of ***GAMP 5 Quality Risk Management Approach*** (May/June 2008), the winner of the 2007-2008 Roger F. Sherwood Article of the Year Award. Martin and Perez were recognized at ISPE's 2008 Annual Meeting, held 26-29 October in Boca Raton, Florida, USA.

Pharmaceutical Engineering established the award to recognize the contribution of authors. Articles are evaluated by a panel of volunteer reviewers according to a number of criteria, concentrating on the importance and timeliness of the subject matter and the quality of the presentation. The criteria for judging is as follows:

- Is it directly useful to the readers in their efforts to improve the industry and themselves?
- Does it improve knowledge/understanding of key topics?
- Is it clear, easy to read? (Low jargon usage)
- Quality of artwork, graphs, etc.?
- Appropriate length?

The finalists for each "Article of the Year" are chosen from the September/October issue of the previous year, through the July/August issue of the current year. The award program was established to express appreciation to all of the authors who submit their work for publication in Pharmaceutical Engineering.

From left to right: Bruce Davis (outgoing ISPE Chairman), Kevin Martion, Randy Perez, and Charles Hoiberg (incoming ISPE Chairman).

Japan Affiliate Successfully Supports ISPE Global Training

The Japan Affiliate validation training course, "Validation for the 21st Century: Concepts, Risk Assessments, and Documentation," was held 29-30 September in Tokyo with ISPE's North American instructor Diana Knittel-Pace.

Final attendance for the training event, that included simultaneous translation and workshop exercises, reached 71 with 11 assistants. The goal was to deliver training in new validation corresponding to the latest guidance issued by US regulatory authorities, including the US FDA.

ISPE Members are now located in 90 countries and spread across most of those with language, economic variations, and local/regional regulatory differences. With limited resources as a not-for-profit Society, ISPE realized that a new delivery method for training materials needed to be developed. With this realization, ISPE developed a collaboration model to provide Affiliates and Chapters with access to the Society's global training body of knowledge. By licensing ISPE course content, Affiliates and Chapters are able to eliminate the need for lengthy content development and provide immediate training to their members and the local industry. For the one-time annual licensing fee under the collaboration model's terms, Affiliates can deliver the course as many times as desired for one year, either in its current two-day format or using the eight course modules for a series of training events to generate additional revenue.

For more information about the Japan Affiliate and events/activities, please visit www.ISPE.org/japan or contact Office Manager Natsumi Sahara by tel: 81-3-3818-6737 or email: ispe-japan@iris.ocn.ne.jp. For more information about ISPE's collaboration model for global training, please contact Director of Training Ali Montes by tel: +1-813-960-2105 ext. 237 or email: amontes@ispe.org.

Technology Based Learning Takes Off at Annual Meeting

Speaker Presents Live from India Via Web

In an important first for ISPE, attendees of last month's *Follow on Biologics – A Panel Discussion* Annual Meeting session interacted with both speakers onsite in Boca Raton, Florida, USA and a speaker broadcast live via Web from Bangalore, India.

"Use of this type of technology to bring Dr. Srinivasan's presentation to Annual Meeting attendees was a great step forward in the Society's ability to educate and get the best speakers to our sessions... I look forward to more opportunities like this."

James Spavins, Vice President Global CMC, Pfizer, Inc.

Raman Srinivasan, PhD, of Biocon, seamlessly conducted his part of the session by a Web-cam system new to ISPE events. Attendees listened to and carried on a discussion with Srinivasan as if he were physically in the same room with the session's other speakers, including Steven Kozlowski, Director, Office of Biotechnology, USA; Anthony Ridgway, Senior Regulatory Scientist, Health Canada; Raymond Arner, Principal, Miller, Canfield, Paddock & Stone PLC, USA; and Session Leader Deepak Agarwal, Director, Pharma Technology, Jacobs Consultancy, USA.

"Use of this type of technology to bring Dr. Srinivasan's presentation to Annual Meeting attendees was a great step forward in the Society's ability to educate and get the best speakers to our sessions," said James Spavins, Vice President Global CMC, Pfizer, Inc. "I look forward to more opportunities like this."

Together the speakers delivered a well-received session exploring the economic, financial, legal, technical, and regulatory issues of biogenerics, biosimilars or follow on biologics. "As far as I am concerned, this was the best session I attended at the Annual Meeting," said Gary Incorvia, ISPE Past President. "The excellent content, along with this enabling technology, takes ISPE educational offerings to an exciting level."

Speaker Web casts are just one of the many ways ISPE plans to use the Web to connect pharmaceutical manufacturing industry professionals worldwide with educational opportunities. Technology based learning in development also includes new live and recorded webinars, Certified Pharmaceutical Industry Professional℠ (CPIP; www.ISPE-PCC.org) webinars, podcasts, audio briefs, and post-event video recordings. Those unable to attend the ISPE 2008 Annual Meeting may access live recordings of the 2008 keynote presentations and five education sessions at www.ISPE.org/annualmeeting:

Keynote Sessions

- Hans Rosling, MD, PhD, Professor of International Health, Karolinska Institute and Director of Gapminder Foundation, Stockholm, Sweden
- Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, U.S. FDA
- Patrick Y. Yang, PhD, Executive Vice President, Product Operations, Genentech, USA

Education Sessions

- Competing in the Global Marketplace
- Planning the Successful BioPharm Facility Modification
- Product Quality Lifecycle Implementation (PQLI) Global Update
- Design Standards for the Pharmaceutical Industry
- ISPE Baseline® Guide – Quality Laboratory Facilities

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
November/December 2008, Vol. 28 No. 6

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.

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

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

Bioreactors/Fermenters

Cleanroom Products/Services

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

Cleanroom Products/Services (cont.)

Dagard USA Corp., 14 Place Des Drs Ch Et Ch Merieux, 69007 Lyon, France. +33-555824000. www.dagard.com. 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.

Filtration Products (cont.)

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.

Astro Pak Corp., 270 E. Baker St., Suite 100, Costa Mesa, CA 92626. (800) 743-5444. See our ad in this issue.

Passivation and Contract Cleaning Services (cont.)

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

Spray Dryers

Heinen Drying Inc., 1504 Grundy's Ln., Bristol, PA 19007. (215) 788-8196. See our ad in this issue.

Sterile Products Manufacturing

Tanks/Vessels

Eagle Stainless, 816 Nina Way, Warminster, PA 18974. (215) 957-9333. See our ad in this issue.

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.

ProPharma Group, 10975 Benson Dr., Suite 330, Overland Park, KS 66210; 5235 Westview Dr., Suite 100, Frederick, MD 21703. (888) 242-0559. 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.

Vial Traying Systems

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

Water Treatment

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

Veolia Water Solutions & Technologies, Global Headquarters, L'Aquarène – 1, place Montgolfier, 94417 Saint-Maurice Cedex, France, www.pharma.veoliawaterst.com, Email: pharma-info@veoliawater.com. See our ad in this issue.

On-Line Exclusive Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
November/December 2008, Vol. 28 No. 6

A Regulator's Perspective of His GAMP Experience

by Anthony Trill, retired MHRA Inspector

Getting Involved in GAMP

I was promoted in 1988 to a specialist role within the Medicines Inspectorate with responsibilities for computerised systems, GMP compliance standards, and inspection aspects. On 9 June 1988 I gave a keynote presentation at an IQA/PQG meeting at the Royal Pharmaceutical Society in London entitled, "Approaches to the Validation of Computer Systems in Quality Assurance." I well remember making use of several props on that occasion, including a large orange from the lunch table which I proceeded to peel. It 'apeeled' (sic) to me during the talk to illustrate different concepts (network – (string) bag of oranges; regulatory orange guide – the skin; modules of software and interdependence – joined segments of fruit with juice therein!). This approach with props had worked well in 'Round Table' debating contests!

In 1988 I also became aware of the work of Tony Margetts and Pat Jeater of ICI Pharmaceuticals through the publication of their paper at Interphex UK entitled, *"Validation of Computer Systems Used in Process Control and Management Information."*

I helped organise an international training and interactive seminar (with the assistance of the Rede Consultancy Group) for inspectors and industry at Keele University in 1989. Part of that exercise was to consider existing GMP guidance for computerised systems (including Chapter 16 of the UK's 1983 Orange Guide) and to formulate early drafting proposals for what would become the new EU GMP Annex 11.

In 1990 at a Concept Heidelberg meeting in Frankfurt, Germany I gave a paper entitled, *"A Medicines Inspector's Views on Validation Requirements for Computerised Systems in the European Drug Processing Industry,"* and first met Dr. Heinrich Hambloch, who was speaking at the same event. Little did I know at the time that we would go on to collaborate with three other authors (including Ken Chapman who participated in the Keele event) on the book, *"Good Computer Validation Practice – Common Sense Implementation,"* by Stokes, Branning, Chapman, Hambloch, and Trill (1994, Interpharm Press, now CRC Press-Taylor and Francis Group ISBN 0935184554).

In 1990/91 I was invited by David Selby and Tony Margetts of the industry focus group Pharmaceutical Industry Computer System Validation Forum (PICSVF) to become a member of their working group as a regulatory representative of MCA. (The EU GMP Annex 11 was published in 1991 and became effective in 1992). The group had the task of improving industry's understanding of regulations for computerised systems and sought to improve communications on these issues not only within the pharmaceutical industry, but also with its suppliers. My work with PICSVF continued in parallel and took account of the findings and requirements of the FDA, MCA, and other regulators, together with issues raised by industry focus groups such as the US PMA, UK IQA/PQG, and lessons from topical national/international standards best practice initiatives and government sponsored reports on software quality standards, i.a.

At that time I was also a regulatory member of the drafting review panel for the TickIT Guide from BCS for DTI. The first edition of the *"Guide to Software Quality Management System Construction and Certification using EN 29001"* was published in 1991. This initiative continues to this day under the auspices of BSI-DISC. My direct involvement continued as a contributor and reviewer over the period 1990-98, issues one to four. I'm pleased to see that the GAMP Forum/COP continues to have steering committee participation in the current TickIT scheme.

In 1991 I also presented a paper entitled, *"British Experience with Computer Systems,"* at the September meeting of the FIP held in Washington DC, USA and had the pleasure of meeting Dr. Ron Tetzlaff of the FDA who was speaking at the same event. I recall it was great to sit with Ron and Ken Chapman and chat over a beer afterwards in informal surroundings.

The first four or five years after my appointment were extremely busy, considering I was supposed to be limited to 20% of my time on the topic. I voluntarily studied for an Open University post-graduate Diploma in Digital Computing in my own time during this period and it was tough to keep up with the tutorials, practical work, and exams whilst travelling overseas and in the UK on inspections. Remember, this was in the days prior to laptops and global broadband connectivity!

The Forum (PICSVF) piloted prototypes of its Validation Management paper (VMAN-II) and consulted with industry in 1992/93. The working drafts and case studies were discussed at several seminars (Banks, Margetts, Casford, and Trill – Management Forum Conferences) and referenced in a trilogy of papers that I published in Pharmaceutical Technology International in February, March, and May 1993 (Trill, A J ., *"Computerised Systems and GMP – A UK Perspective etc,..."*). Rather than referring to a PICSVF-VMAN document (which did not exactly trip off the tongue) I informally suggested that the initiative should be encapsulated by the term 'GAMP' (Good Automated Manufacturing Practice) having suggested that we could use 'GMP' plus a suitable vowel!

Thus, in 1994 the approved version of the VMAN document (Validation of Automated Systems in Pharmaceutical Manu-

A Regulator's Perspective of His GAMP Experience

Continued.

"Following acquisition by ISPE, the GAMP Forum movement has gone from strength to strength from a national to an international organisation with a well-respected set of principles and guidelines that continues to evolve and spread as a credible de-facto international standard, or benchmark, of good practices in this challenging field."

facturing) was formally launched at the QEII Conference Centre in March 1994 at a Management Forum sponsored conference entitled PICSVF, Good Automated Manufacturing Practice in the Pharmaceutical Industry (GAMP), with the guidelines being published at that time by Logica Industry Ltd. In addition to myself and a number of GAMP Forum leaders, there were many eminent national and international speakers at this conference. It was a landmark event aimed at achieving a shared understanding and consensus within the pharmaceutical business community (suppliers, purchasers, developers, and users) and regulatory bodies of good automated manufacturing practice in the mid-1990's. (See also Chapter 13 of the 1994 *"Good Computer Validation Practices…"* book referenced above for more details of this event).

I spoke together with Tony Margetts at an APV Conference in 1994 in Darmstadt, Germany about *"Computerised Systems, GMP, Electronic Batch Records and GAMP."* The following year I published a paper in *Pharmaceutical Engineering* mapping current GMP to GAMP sections and I presented a paper in Basel, Switzerland at a conference hosted by Coopers and Lybrand covering *"Pharmaceutical Manufacturing and GMP requirements for Automated Systems."*

In 1996 we took GAMP to Baltimore, Maryland, USA, to the Computer Related System Validation Conference jointly sponsored by ISPE and PDA, where there were a number of papers from GAMP exponents and I gave a sagely opinion entitled, *"An MCA View of the Presented Initiatives."*

At a fairly early stage we had recognised that GAMP needed the active participation of the supplier community if the industry was to be able to leverage the knowledge and skill of the developers of the proprietary equipment, software, and systems. To facilitate this, A Supplier Forum was established initially as a Special Interest Group within GAMP, and due to its success and synergy, ultimately became part of the main body of the GAMP Forum with representation on steering committees.

Since the mid 1990s I have had the pleasure of collaborating with Guy Wingate (Editor and lead author) together with numerous GAMP Forum expert authors in compiling two eminent text books in the field (1997 and 2004 Interpharm Press – CRC Press, Taylor and Francis Group). I met Guy - an outstanding exponent of validation and compliance in this field – initially through my GAMP contact with ICI Eutech Engineering Solutions and the supplier community.

The rest, as they say, is history. Following acquisition by ISPE, the GAMP Forum movement has gone from strength to strength from a national to an international organisation with a well-respected set of principles and guidelines that continues to evolve and spread as a credible de-facto international standard, or benchmark, of good practices in this challenging field. It is pleasing to note the GAMP communities now across so many continents: Americas, Europe (UK, Nordic, D-A-CH, Francophone and Italia), and Japan. Maybe other Asian countries, Australasia, and other Eastern European countries will actively participate in GAMP COPs in the next few years.

From the mid 1990s I was also a member of the Government's Interdepartmental Group that met periodically to consider critical software engineering issues (ICSE) across national government sectors, both civil and military. Later in the 1990s and early 2000s I was an active member of the DTI User Group for information security management systems (ISMS) and the BS 7799 standards and codes of practice. This evolved internationally to ISO/IEC 17799 and now ISO/IEC 27001. This informed the work I was contributing to GMP, PIC/S, and GAMP initiatives.

I recall speaking from the floor of one of our GAMP launch-related Amsterdam seminars suggesting constructive ways to counter some of the questionable requirements implicit within proposed regulations from the FDA concerning electronic records and signatures. In 1999 I can well recall video conference exchanges that I had with Paul Motise (FDA) at a London Business Intelligence Conference debating some of the finer philosophical points behind what became 21CFR part 11. Paul clearly had very strong views on these matters. Subsequent collaborative work within GAMP Forum, ISPE, PDA, and the FDA has helped to move this debate on to a more pragmatic plane.

I have been privileged to work constructively with the GAMP Europe Steering Committee and helped to facilitate a number of new topics for Special Interest Groups, whilst contributing to and reviewing editions one to five of the GAMP Guide (together with a number of the good practice guides and working papers) from a regulatory perspective over the years. I have always tried to build bridges between different interests and focus groups to confront and resolve difficult issues whilst recommending the adoption of established best practices from other disciplines. I should like to thank Robert Best, David Selby, Guy Wingate, Gert Moelgard, Sion Wyn, Peter Robertson, Tony Margetts, Chris Clark, Chris Reid, Heinrich Hambloch, Hartmut Hensel, Yves Samson, Kate Samways, Randy Perez, Paige Kane, Mark Cherry, Sam Brooks, Carlo Bestetti, Anders Bredesen, Peter

A Regulator's Perspective of His GAMP Experience

Continued.

Coady, Sandro de Caris, Mark Foss, Niels Holger Hansen, Scott Lewis, Rob Stephenson, Paul D'Eramo, Rory Budihandojo, Makoto Koyazaki, Kenichi Ogihara, Gloria Hall, Gail Evans, Pol van De Perre, and all past and present members of GAMP Steering Committees and Council for their professional collaboration and friendship over the years. Long may it continue!

Accomplishments and Lessons Learned from the Field

I had the opportunity to lead the PIC/S Expert Circle on Computerised Systems for a number of years and in that time we not only arranged many different training events for inspectors but compiled various documents, including *PI011 "Good Practices for Computerised Systems in Regulated 'GxP' Environments" (PICS 2003)* which has the status of a training guide for Inspectors and "*'Straw Man' project revised versions of PIC/S GMP Chapter 4 (Documentation) and Annex 11 (Computerised Systems)" (PIC/S 2006).* These PIC/S documents have been the inspiration and justification for the subsequent EU Concept paper proposing revisions to the corresponding EU GMP Chapter 4 and Annex 11.

Following the publication of the EU Concept paper to revise EU GMP Chapter 4 and Annex 11, I became the lead MHRA Inspectorate member of the EU GMP revision drafting team and Co-Rapporteur. This enabled some continuity with the earlier PIC/S work. Drafts from our revision drafting team were subjected to further review and editing by the EU Ad-Hoc GMP Inspectors Working Party prior to publication for wider comment. The resulting first draft of each revised document was published 11 April 2008 by the EU Commission for public commenting. There are doubtless some editing, contextual and omission errors. There may also be opportunity for additional material to be incorporated in Chapter 4 and possibly in Annex 11, particularly where it may be applicable across 'GxP.'

The pre-existing versions of Chapter 4 and Annex 11 are outdated and do not address current issues for systems or electronic records. Whilst it is recognised that it is difficult to make the revised documents 'future proof' for computerised systems, electronic documents, records and data processing (due to the rate of change with the technology and scope of applications), the new documents are a considerable advance on the old material with its roots in the late 1970s and 80s!

It is easy to criticise requirements in a GMP document; more difficult to draft forms of words as a solution that will satisfy all sensibilities across a multi-lingual business and regulatory community.

However, with good will, common sense, and objectivity it should be a 'win-win' result for regulators and all stakeholders alike, across the 'pharmaceutical business spectrum' so that whilst compliance improvements are achieved, we also ensure that industrial innovation is facilitated.

Coming Full Circle

In my last 3 months with the Agency I worked on a part-time basis (20%) on specific projects, to acclimatise to eventual retirement. I retired fully from the MHRA in July 2008. A barrel of oil cost $147 and I decided to sell my 2.5 Litre Volvo. A fine start!

I have been relaxing and reflecting for some months but the economic downturn has come as quite a shock! I am looking forward to an improved work-life balance but may eventually be open to a measured amount of professional project work either as an Associate, Partner, EU Qualified Person, Consultant, Advisor or Auditor where I think I can add value. Alternatively I shall be quite happy to relax and enjoy life with my family as we now have three grandchildren. Our most recent Granddaughter was born in October! At time of revising these notes a barrel of oil has now come down to $43 and even with a somewhat devalued GB Pound there is now the prospect of travelling again, for leisure, by car.

Before I retired fully I thought it was quite possible that projects in the near term might include a consideration of (funds permitting): various potential ball related hobbies, completing pending home improvements, reading, writing, speaking, walking, photography, painting, the performing arts, dancing, and gardening, improving physical fitness, fly-fishing, sailing and politics. Early days yet but I have initiated some of these!

It occurred to me that I might also have some time to consider some off-the-wall business related entrepreneurial feasibility projects such as winemaking or brewing. I already have *"The Microbrewers Handbook"* and *"A Guide to Craft Brewing"* – so if there are other potential partners for a new or existing micro-brewery investment out there, then let me know! However, with the current demise of both small and large businesses I think this now unlikely to be viable.

I hope to maintain my active involvement with ISPE GAMP COP through international committee participation and other work if possible. I have attended two GAMP Europe steering committee meetings since retiring. I have a lot of "GAMPer" and ISPE friends and would like to stay in touch.

Apart from complex, challenging, pharmaceutical inspection related work in general, I have a particular interest in the revision of GMP Annex 11 and Chapter 4 and I see them to some extent as part of my legacy. It seems that we have now come full circle: When I started in this specialist role with MCA 20 years ago I was involved with others in helping to establish the first Annex 11 for the EU GMP set and low and behold, as I leave MHRA we are in the throws of creating new versions of Annex 11 and Chapter 4 fit for the next 10 to 20 years. Good timing or what? Good luck to the new generation. Build bridges, achieve consensus, move forward, add value to the guidance and make it work!

On-Line Exclusive Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
November/December 2008, Vol. 28 No. 6

Argentina

Illicit Use of Ephedrine

Argentina's National Medicines, Food and Medical Technology Administration (ANMAT), has issued new rules effective from 21 August 2008 to prevent illicit use of ephedrine. In order to reduce illicit production and sale of any drugs containing ephedrine and pseudoephedrine (e.g., methylamphetamine), the ANMAT regulatory agency has strengthened importation regulations.

New regulations to be followed by any wholesalers or holders of certificates for medicinal products containing these active substances include a request for an importation authorization to the Narcotics and Psychotropics Department of ANMAT's National Institute of Medicines. The applicant also will need to provide detailed information to the ANMAT on any ephedrine or pseudoephedrine products imported, for instance, importer's name and legal address, the substance to be imported, the quantity in salt and in base kilograms, the pharmaceutical form (number of units, concentration), the manufacturer's details, the point of entry into Argentina, the means of transportation, and the reasons for the importation.[1]

Immunobiologicals Transfer between Regions

A new regulation released by the ANMAT agency was introduced in early 2008 with the intention to facilitate the immunobiologicals transfer between Argentinean regions.

This new procedure is solely for batches manufactured under the new National Program for the Official Production of Medicinal Products and Vaccines Laboratories. The aim of this program is to improve the access to medicines.[2]

Australia

In response to the government's focus to change and update the Australian regulatory framework for therapeutic goods, the Therapeutic Goods Administration (TGA) proposed a reform agenda at Parliament House. Among the proposed initiatives is a new fee that will be charged only per inspection instead of the current annual fee. According to the TGA, this proposal (expected to come into effect in July 2009) is meant to enhance the transparency and predictability of costs.
In addition, the TGA planned to develop a "manufacturing master file" in consultation with the industry.

The TGA is also considering levying additional conditions on GMP licenses in a view to allow the regulatory agency to take samples of any substance or material used in the manufacture of a medicine or a medical device.[3]

Canada

The Canadian industry has outlined views on changing and updating the regulatory framework for biosimilars during Health Canada's Biologics and Genetic therapies Directorate that took place in June 2008. Until now, biosimilars were treated the same way as conventional generic drugs from a regulatory point of view. According to this outcome, biosimilars will need to have an abbreviated data package. In addition, following manufacturing changes approved biosimilar products will need to be compared only with itself and not with the reference product.[4]

India

National Biotechnology Regulatory Authority

The Indian government plans to set up a National Biotechnology Regulatory Authority (NBRA) as an independent body which would review and regulate all drugs, medical devices and combination products that have a biological component. The branch of the agency involved in regulating genetically modified human and veterinary health would be overseeing the clinical trials processes, premarket safety assessment, product approval, and post market monitoring. The establishment of the NBRA has required new legislation to be developed – the National Biotechnology Regulatory Act, 2008. Online comments on the proposed legislation and the department's draft plan on the NBRA were due by 31 July. Currently, the regulation for biotechnology products are spread over multiple acts which may be amended after the compilation of the new regulation.[5]

New Pharmaceutical Policy Department

A new Department of Pharmaceuticals has been created under the Indian Ministry of Chemicals and Fertilizers to coordinate a range of activities, such as the promotion and coordination of national and international research, development of infrastructure, manpower and skills for the sector, conducting public-private partnerships, exchange of information and technical guidance on all pharmaceutical-related matters, and assisting in the planning, development, and control of related industries. This new department is also responsible for all matters relating to the National Pharmaceutical Pricing Authority (NPPA), including functions of price control and monitoring. The NPPA is seeking the public's help in an effort to gather evidence against drugmakers accused of overpricing their products. In addition, the department also has agreed that financial grants be provided to the pharmaceutical sector for research projects involving clinical trials (Phases I, II, and III) to develop new drugs for neglected tropical diseases, such as tuberculosis, malaria, filariasis, and leishmaniasis, which affect the Indian sub-continent.[6]

China

China's State Council has published a white paper outlining the steps the country has implemented in the last few years to improve the regulation of pharmaceuticals. The document is mostly a review of various legislative and administrative changes and current systems with a strong emphasis on drug safety measures. Steps to improve product monitoring and facility inspections have led to a "considerable improvement" in this area. Around 7,400 batches of chemical drugs were tested last year, of which 98 percent met current standards, while a batch release system for blood products was introduced at the beginning of this year. With these new systems, the number of adverse drug reaction reports

reached 400 per million people in 2007, a ratio the report claims is close to that of more industrialized countries.[7]

United Kingdom

The UK MHRA is seeking comments on proposals to exempt from European advanced therapies legislation (No 1394/2007) hospitals that prepare Advanced Therapy Medicinal Products (ATMPs) on a non-routine basis for individual patients. The agency is also seeking views on changes to the UK "Specials" scheme (in accordance with European Directive 2001/83/EC on human medicines), which applies to unlicensed medicinal products (including ATMPs) commissioned by healthcare professionals to meet the special needs of individual patients.

Under the hospital exemption scheme, the manufacture of ATMPs would have to be authorized by the MHRA and the product would have to be used within the UK. Such products would have to meet the same traceability, good manufacturing practice, patient information, ethics, and pharmacovigilance standards as those ATMPs that were granted a centralized marketing authorization by the European Medicines Agency. The MHRA is recommending that the specific proposals in these areas also should apply where ATMPs are supplied under the Specials scheme, because of the similarity between the kinds of activities under both schemes. The MHRA also would conduct risk-based inspections of hospitals under the exemption scheme. The MHRA notes that existing European pharmacovigilance requirements (as laid out in Regulation (EC) No 726/2004, as well as in the ATMP regulation) would not apply to unlicensed products under the exemption scheme, and that it would not be realistic to expect periodic safety update reports for products produced on a non-routine basis. The agency is proposing that under the hospital exemption scheme, pharmacovigilance requirements would cover the notification of adverse reactions and submission to the agency of a risk management plan, together with a manufacturing license application. The MHRA has proposed to adopt traceability requirements for ATMPs that are similar to those requirements laid out in the European directives on tissues and cells (Directive 2004/23/EC) and blood (Directives 2002/98/EC). These directives require manufacturers to keep traceability records from the beginning of a product's development to its dispatch to the user (in this case, a hospital). With regard to labeling, special warnings should be included, in addition to a manufacturing authorization number, batch numbers and unique patient identifier numbers.[8]

United States

Quality Information

The FDA plans to launch a pilot program for the submission of quality information (chemistry, manufacturing, and controls) for complex biotechnology products. This program intends to provide more insight into the agency's review of Quality By Design (QbD) and risk-based approaches for manufacturing such products. Pharmaceutical companies that want to take part should submit their requests by 30 September 2009. The agency intends to develop guidance for industry on QbD and risk management in pharmaceutical manufacturing. The principles of this new approach are based on several International Conference on Harmonization guidance documents: Q8 – Pharmaceutical Development, Q9 – Quality Risk Management, and Q10 – Pharmaceutical Quality System.[9]

cGMP Requirements for Phase I Investigational Drugs

The US FDA has decided to exempt most drugs and biologics involved in Phase I clinical trials from certain current Good Manufacturing Practice (cGMP) regulations. In a final rule that comes into effect on 15 September, the agency says that the exemption should facilitate the initiation of investigational clinical trials in humans, while continuing to protect human subjects. It is expected to streamline and promote the drug development process. The agency says that its cGMP rules for commercially manufactured products are typically characterized by large, repetitive, commercial batch production. This may not be appropriate for investigational drugs used for Phase I trials. For example, rotation of the stock for drug product containers, the repackaging and relabeling of drug products, and separate packaging and manufacturing areas are generally not of concern for the limited production of Phase I investigational drugs. Also, the requirement for fully validated manufacturing processes may not be appropriate for this early stage of drug development. However, the FDA can initiate action to seize an investigational drug if its production does not occur under conditions sufficient to ensure identity, strength, quality and purity, which may adversely affect its safety.[10]

Product Information and Labeling

A controversial new rule has been released by the US FDA that mentions when drugs and medical devices labeling can be updated through a Changes Being Effected (CBE) supplement by manufacturers in advance of approval by the FDA.

This new rule came into force on the 22 September 2008 and manufacturers have criticized this new rule claiming that it limits the situations when they need to amend the labeling quickly and provides sponsors immunity from failure-to-warn lawsuits.

In response to this, critics of the FDA said manufacturers will have to decide on whether to submit a CBE supplement or any other type of additional documentation to the agency, adding that failure to update labeling as required could result in regulatory actions or criminal penalties.[11]

United States – Vietnam Bilateral Cooperation

A memorandum of understanding between the US and Vietnam became effective on 24 June which aims to improve the safety of food, drugs, and medical devices being traded between the two countries. This three year agreement ensures that quality is built into every step of the product lifecycle. It involves the exchange of information

on regulatory systems, including details on laws and regulations; guidance documents; lists of drugs approved by the FDA for use in agriculture; training opportunities on key topics such as pharmacovigilance; and timely information on potential or emerging issues of product safety (e.g., contamination).[12]

Europe

Multilateral Cooperation: EU, Australia, and US to Coordinate Inspection Planning

The European Medicines Agency has published a proposal under which regulators in the European Union, the US, and Australia would coordinate the international planning of pharmaceutical manufacturing inspections. The proposal outlines a one-year, tripartite pilot program that aims to make more efficient use of global good manufacturing practice inspection resources. Under the pilot, each regulator would exchange inspection schedules and other information, such as whether they have previously inspected a site or whether they have an interest in a site for some other reason. Following a review of each other's information, a teleconference would be set up to see whether a joint inspection could be organized, whether one of the inspectorates could perform a planned inspection and provide results to the other parties, or whether one of the parties would undertake to cover the activity of interest to the others.

The EMEA notes that in future, the EudraGMP database will allow certain GMP information on inspections performed by all European Economic Area member states, as well as from mutual recognition agreement partners and other international partners, to be accessible. A further release of the database includes a module for sharing inspection plans. The first phase of the database was launched in May 2007.[13]

Herbal Medicinal Products

The GMP Annex 7 on the manufacture of herbal medicinal products has been revised with the intention of specifying application of GMP provisions for active substances used as starting materials (Part II) for the manufacture of herbal medicinal products. Additional changes are specifically to the new Directive 2004/24/EC on traditional herbal medicinal products.

The new Annex will come into effect on 1 September 2009.[14]

Radiopharmaceuticals

Annex 3 relating to the Manufacture of Radiopharmaceuticals has been revised to include the new GMP requirements for actives substances used as starting materials (GMP Part II) and GMP aspects for radiopharmaceuticals. This new Annex will come into effect on the 1st March 2009.[15]

References

1. Anmat Disposition 4712/2008, *Boletín Oficial de la República Argentina,* No 31.471, 20 August 2008, referenced in RAJ Pharma in October 2008.

2. Anmat Disposition 4932/2008, *Boletín Oficial de la República Argentina*, No 31.477, 28 August 2008.

3. TGA, Regulatory Reform Program and Information about Consultations held in July/August, 2 September 2008, www.tga.gov.au/regreform/index.htm.

   TGA, Stakeholder Consultation, 24 July 2008 www.tga.gov.au/regreform/080724prespm.pdf, referenced in RAJ Pharma in October 2008.

4. Summary report of the consultation on the Regulatory Framework for Subsequent Entry Biologics, 5-6 June 2006, www.hc-sc.gc.ca/dhp-mps/pubs/biolog/2008-consult-sebpbu-rep-rap/index-eng.php, referenced in RAJ Pharma in September 2008.

5. Referenced in RAJ Pharma in August 2008:
   - Government of India, Department of Biotechnology, http://dbtindia.nic.in/NBRA/NBRA.htm.
   - Draft establishment plan for setting up of NBRA, http://dbtindia.nic.in/NBRA/Draft%20establishment%20plan%20for%20NBRA_28may2008.pdf.
   - Draft National Biotechnology Regulatory Bill 2008, http://dbtindia.nic.in/NBRA/Draft%20NBR%20Act_%2028may2008.pdf.
   - Press Information Bureau press release, 28 June 2008, http://pib.nic.in/release/release.asp?relid=39892.

6. Referenced in RAJ Pharma in August 2008:
   - NPPA, Public Notice, 9 July 2008, http://nppaindia.nic.in/order/notice-9-7-08.html.
   - NPPA, List of pending cases of overcharging, 9 July 2008, http://nppaindia.nic.in/order/listpendingcases.html.
   - Press Information Bureau press release, 26 June 2008, http://pib.nic.in/release/release.asp?relid=39812&kwd.

7. Referenced in RAJ Pharma in August 2008:
   - Chinese State Council, 18 July 2008, http://english.gov.cn/2008-07/18/content_1049011.htm.
   - *The Regulatory Affairs Journal – Pharma*, 2007, 18 (8), 550.

8. MHRA public consultation MLX 353 on advanced therapy medicinal products, 23 July 2008, www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/MLXs/CON020714, referenced in RAJ Pharma in October 2008.

9. - *Federal Register*, 2 July 2008, 73 (128), 37972-37974, www.fda.gov/OHRMS/DOCKETS/98fr/E8-14999.pdf.
   - Sam T, Potter C, Berridge J, Design Space – Promoting Quality by Design, *The Regulatory Affairs Journal - Pharma*, 2007, 18(1), 7-14, referenced in RAJ Pharma in October 2008.

10. Referenced in RAJ Pharma in October 2008:
    - Federal Register, 15 July 2008, 73 (136), 40453-40463, www.fda.gov/OHRMS/DOCKETS/98fr/E8-16011.pdf.
    - FDA press release, 18 July 2008, www.fda.gov/bbs/topics/NEWS/2008/NEW01863.html.
    - FDA, Guidance for Industry: Current Good Manufacturing Practice for Phase I Investigational Drugs, 15 July 2008, www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2005-D-0157-gdl.pdf.
    - Federal Register, 15 July 2008, 73 (136), 40584-40585, www.fda.gov/OHRMS/DOCKETS/98fr/E8-16002.pdf.

11. Referenced in RAJ Pharma in October 2008:
    - Federal Register, 22 August 2008, 73 (164), 49603-49610, www.fda.gov/OHRMS/DOCKETS/98fr/E8-19572.pdf.
    - Law firm Duane Morris, Alerts, 27 August 2008, www.duanemorris.com/alerts/alert2955.html.
    - AAJ press release, 21 August 2008, www.justice.org/PressRoom/PressReleases/2008/aug21.aspx.

12. US Department of Health and Human Services, 24 June 2008, http://hhs.gov/news/press/2008pres/06/20080624a.html, referenced in RAJ Pharma in October 2008.

13. EMEA press release, 22 July 2008, www.emea.europa.eu, and HHS press release, 9 July 2008, www.hhs.gov/news/press/2008pres/07/20080709a.html.

14. European Commission, September 2008, http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/vol4_an7_2008_09.pdf.

15. European Commission, September 2008, http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/2008_09_annex3.pdf.

Supplement to
PHARMACEUTICAL ENGINEERING®

Facility of the Year Awards

OVERALL WINNER

2008

Facility of the Year Awards
OVERALL WINNER

Pfizer Manufacturing Deutschland GmbH

ENGINEERING PHARMACEUTICAL INNOVATION

ISPE®

www.ISPE.org

Table of Contents

Cover Photograph

Photo courtesy of Pfizer Manufacturing Deutschland GmbH.

Supplement to
PHARMACEUTICAL ENGINEERING®

2008 Facility of the Year Awards

Articles

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, China 200041
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

ENGINEERING
PHARMACEUTICAL
INNOVATION

ISPE would like to thank the following Facility of the Year Category Winners' key project participants for their generous advertising support which made this Supplement possible.

Advertiser's Index

www.facilityoftheyear.org

The 2008 Facility of the Year Awards

The Facility of the Year Awards (FOYA) program, sponsored by ISPE, INTERPHEX, and *Pharmaceutical Processing* magazine, recognizes state-of-the-art pharmaceutical manufacturing projects that utilize new and innovative technologies to enhance the delivery of a quality project, as well as reduce the cost of producing high-quality medicines.

Now entering its fifth year, the annual FOYA Awards program effectively spotlights the accomplishments, shared commitment, and dedication of individuals in companies worldwide to innovate and advance pharmaceutical manufacturing technology for the benefit of all global consumers.

Each of the 2008 submissions was reviewed by an independent, blue-ribbon judging panel of global representatives from the pharmaceutical design, construction, and manufacturing sectors, including:

- **Andy Skibo, *Judging Panel Chair*** - Senior Vice President of Global Engineering, MedImmune
- **Jim Breen** – Vice President of Project Management, Johnson and Johnson
- **Chaz Calitri** – Senior Director of Global Engineering, Pfizer
- **Andrew Ellis** – Vice President of Engineering & Technology of Consumer Healthcare, GSK
- **Christian Ilsøe** – Vice President of Quality & Validation Assurance, NNE
- **Brian Lange** - Director of Engineering, Merck & Co.
- **Geoff Monk** – Vice President of Global Engineering Services, Schering Plough
- **Shinichi Osada** – Chief Marketing Manager, Pharma, Hitachi/Ind Plants Div
- **Jon Reed** – Vice President of Corporate Engineering, Genentech
- **Ron Trudeau** – Vice President of Facilities Engineering, Baxter Healthcare

Pharmaceutical Engineering Focuses on Winners

This Supplement to *Pharmaceutical Engineering* was developed specifically to highlight the remarkable features and technologies of the company selected as the Overall Winner of the 2008 Facility of the Year Awards program.

The following pages also will take you behind the construction and competition curtains, featuring the Category Winners' and the FOYA Judging Panel's thoughts on:

Challenges in Facility Design

- Cost pressures
- Time pressures
- Fast-changing market demands
- Advances in science and technology
- Fewer blockbusters, more custom, lower volume drugs
- Manufacturing flexibility more critical
- Many newly discovered pharmaceutical actives from research are highly potent
- Decreasing direct labor costs

Trends in Facility Design

- Automation
- Quality by Design and science- and risk-based approaches
- PAT
- Lean manufacturing concepts
- Use of model simulation software
- Use of skid mounted equipment
- Streamlined C&Q
- Integrating different functions in one building, fostering close interaction
- Multi-purpose facilities
- Multi-product processing
- Built flexibility, allowing fast and cost-efficient adjustments to accommodate new technologies without major renovation work
- End user/shop floor operator involvement early in project

2009 Facility of the Year Award Call for Submissions

Does your company have a new or renovated facility that's best in its class? Has your firm recently designed, built, or renovated a state-of-the-art pharmaceutical or biotechnology facility? If so, submit an entry for the 2009 Facility of the Year Awards program and your firm may win the coveted 2009 Facility of the Year Award.

In addition to sharing your innovative ideas and lessons-learned with peers, your company will receive the benefit of high-profile media coverage in *Pharmaceutical Processing* magazine, at international INTERPHEX events, at all 2009 ISPE events, and right here in *Pharmaceutical Engineering* magazine. Past winners have obtained press attention and extensive coverage from other worldwide industry publications.

The submission deadline for the 2009 awards program is **1 December 2008**. Detailed eligibility and submission information can be obtained by downloading the 2009 Submission Package available at www.facilityoftheyear.org.

Overall Winner – 2008 Facility of the Year Award

Pfizer Manufacturing Deutschland GmbH

Containing a New Era in Pharmaceutical Manufacturing

by Rochelle Runas, ISPE Technical Writer

A few years ago Pfizer Manufacturing Deutschland GmbH in Illertissen, Germany began working on the answer to the question: Can we push a button once to start the process and several hours later – without any human intervention – receive film coated tablets?

The answer materialized in 2007 in the form of an elegant, futuristic facility housing one of the most intelligent pharmaceutical production plants in the industry. The facility, named the New Containment (NEWCON) Facility for Oral Solid Dosage, is this year's Overall Winner of the 2008 Facility of the Year Award.

NEWCON exterior view.

NEWCON turned unconventional processing concepts – including the single-room concept, high automation requiring no operator interface, and PAT applications – into a safe and efficient manufacturing reality for the production of the smoking cessation product Chantix®.

In an era where industry faces cost and time pressures and changing market demands, Facility of the Year Award judges viewed NEWCON's achievements as innovative, resourceful, and pioneering, not only in containment production, but in the entire field of pharmaceutical manufacturing.

Pfizer Manufacturing Deutschland GmbH

Overall Winner (and Category Winner in Process Innovation)

Project: New Containment Facility for Oral Solid Dosage (NEWCON)
Location: Illertissen, Germany
Architect: PhC PharmaConsult, Heidelberg
Consultant: PhC PharmaConsult, Heidelberg
Construction Manager/Project Manager: Hans Sägmüller, Pfizer Illertissen
Size: 83,958 sq. ft. (7,800 sq. m.)
Cost: US $55 million (39 million Euros)
Product: Chantix®/Champix®
Key Project Participants:

Axima	Glatt	Koppenhoefer and Partner
Comecer	IMA	Rotan
GE Fanuc	Imtech	Servolift
Gerteis		

A Market-Driven Decision

In 2005, Pfizer Manufacturing Deutschland GmbH in Illertissen, Germany was provided with a preliminary sales forecast projecting a rising demand for Chantix® (European product name: Champix®), a smoking cessation product with the active pharmaceutical ingredient varenicline, which helps adults quit smoking by reducing smoking cessation withdrawal symptoms and the craving for cigarettes.

Pfizer manufactures varenicline in Little Island, Ireland, and at the time was conducting secondary production (tablets) at Pfizer Illertissen's pilot containment facility, Illertissen Containment (ICON).

"It became crystal clear that our existing

Continued on page 6.

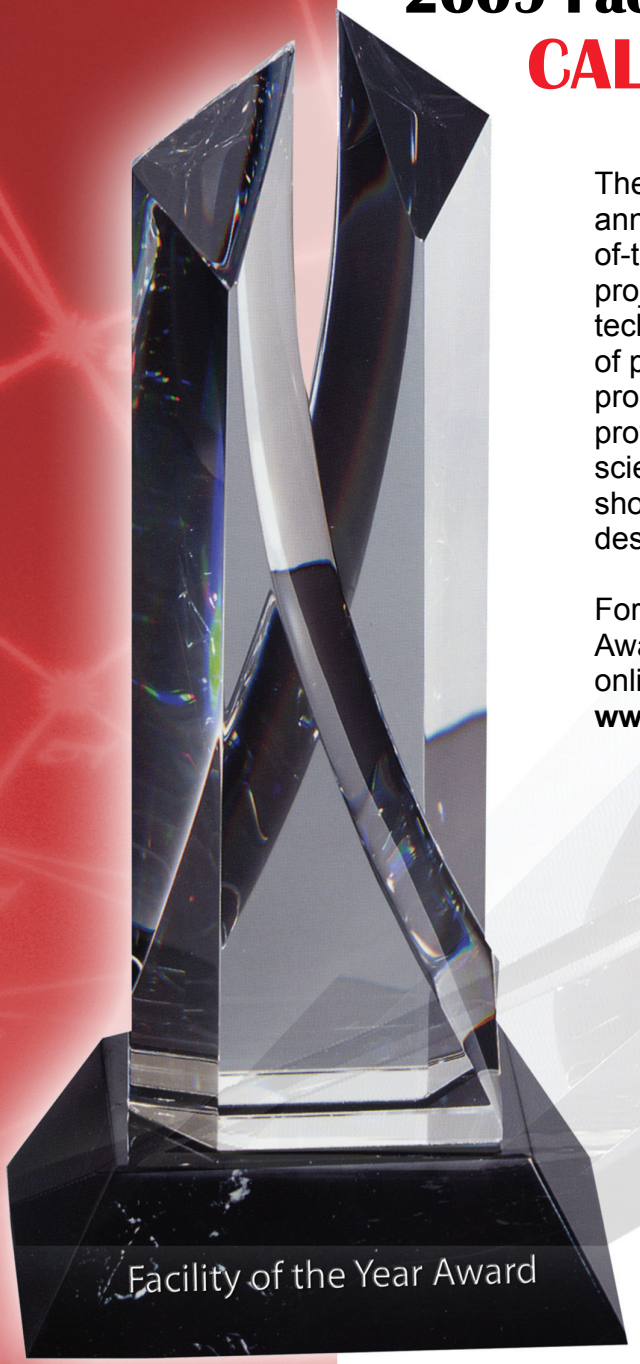
Deadline for Submissions 1 December 2008

2009 Facility of the Year Awards

Awarded by ISPE, INTERPHEX, Pharmaceutical Processing

2009 Facility of the Year Awards

CALL FOR ENTRIES



The Facility of the Year Awards are an annual program that recognizes state-of-the-art pharmaceutical manufacturing projects utilizing new and innovative technologies to improve the quality of projects and to reduce the costs of producing medicines. This unique program provides a platform for the pharmaceutical science and manufacturing industries to showcase their accomplishments in facility design, construction, and operation.

For additional information about the Awards program, and access to the online submission form, visit **www.facilityoftheyear.org.**

ISPE
ENGINEERING PHARMACEUTICAL INNOVATION

INTERPHEX™

Pharmaceutical processing

www.facilityoftheyear.org

Single containment module.

"Driven by the urgent need for greater production capacity, in 2005, Pfizer Illertissen embarked on the design for the NEWCON project.

...the 7,800 sq. m. facility was completed in late 2007 after a construction period of just 25 months."

AGV transport to a unit operation.

pilot containment facility would not be in the position to support the lifecycle of this product and was never intended to," said Holger Weyhers, PhD, Director of Production, Pfizer Manufacturing Deutschland GmbH.

Driven by the urgent need for greater production capacity, in 2005, Pfizer Illertissen embarked on the design for the NEWCON project. Time pressure was further intensified by the successful launch of Chantix® in the US the following year, pushing up the project completion date by six months. Nevertheless, the 7,800 sq. m. facility was completed in late 2007 after a construction period of just 25 months.

Pioneers in Containment Manufacturing

Pfizer Illertissen, which specializes in the oral solid dosage form production of highly potent compounds involving complex containment requirements, was already breaking new ground in containment manufacturing at its ICON pilot facility.

During the first planning phase of ICON, Pfizer Illertissen was faced with a challenge that is increasing in frequency in the pharmaceutical industry: many newly discovered pharmaceutical actives from research are highly potent, requiring extraordinary measures to protect the production staff and the environment.

Instead of opting for the usual spatial isolation of individual process stages and using conventional, physically demanding protective suits with external supply, ICON designers developed a single-room concept in which all contained production equipment was located in a single high containment module and largely automated.

The safe inward and outward transportation of the substances and products are ensured by vacuum systems and split-valve containment technologies. Inside the production area, laser-controlled, driverless transport vehicles move the containers with the materials to the weighing and granulation area, to the tablet press, and to the coaters.

All process stages are controlled and monitored from a separate control center so that employees do not come into contact with any dust that might be generated during the tablet production run.

This novel containment concept was put into operation in ICON in 2003 and served as the prototype for the NEWCON project. "We already had established the design and operational principles for containment manufacturing," said Weyhers. "We simply kept what was good."

Lessons in Automation

While the initial focus of NEWCON's design was on operator safety, the road to that goal also led planners to improving the operational efficiency attained in ICON.

While largely automated, at ICON, the operator needs to trigger the next process sequence. "Operators need to go to their personal computer and program specific directions into the system," said Georg Bernhard, Director, Right-First-Time, Pfizer Global Manufacturing. "For example, 'pick up the bin from location A and bring it to location B.' Once that transfer is finalized, then you program in, 'mix for nine minutes, etc.'"

At NEWCON, the process is completely automated. "We had

all the logic of the sequence," said Bernhard. "You push the button, everything starts on its own, and at the end you have the tablet. Operators supervise the entire process from a control center. This frees operators up from this kind of work."

One area is which automation did not work as well was in the weighing and dispensing of micronized API. "Micronized API causes problems with commercial off-the-shelf equipment," said Bernhard. "Maybe it needed to be coarse. But to build a solution would have taken too long. We tried feeders, different solutions, and in the end opted for a manual process for this part in NEWCON."

While automation was a significant aspect of the NEWCON project, Weyhers recommends not over-engineering. "Avoid being trapped in automation. I'm a fan of operators being able to intervene if they have to. If something goes wrong, you have the opportunity at least to switch to a manual mode. Otherwise, you're in deep trouble."

A dual operator interface was implemented with the main portion at the control center and a second interface at line in case of at worse events so that operators are in a position to do something directly with the equipment, said Weyhers.

Notes from the Judging Panel – What Impressed Them

This project used the ICH concepts of Design Space as the basis for a unique approach to process innovation. PAT applications were installed at key process steps to support adaptive process control. A single containment module houses all process equipment for the production of the dosage form. All internal containment transport is handled by an automated laser AGV system. Material transport is also integrated into the AGV system. The installation has achieved a Design Exposure Limit that does not require the use of PPE, as the automation level is designed for no operator interface.

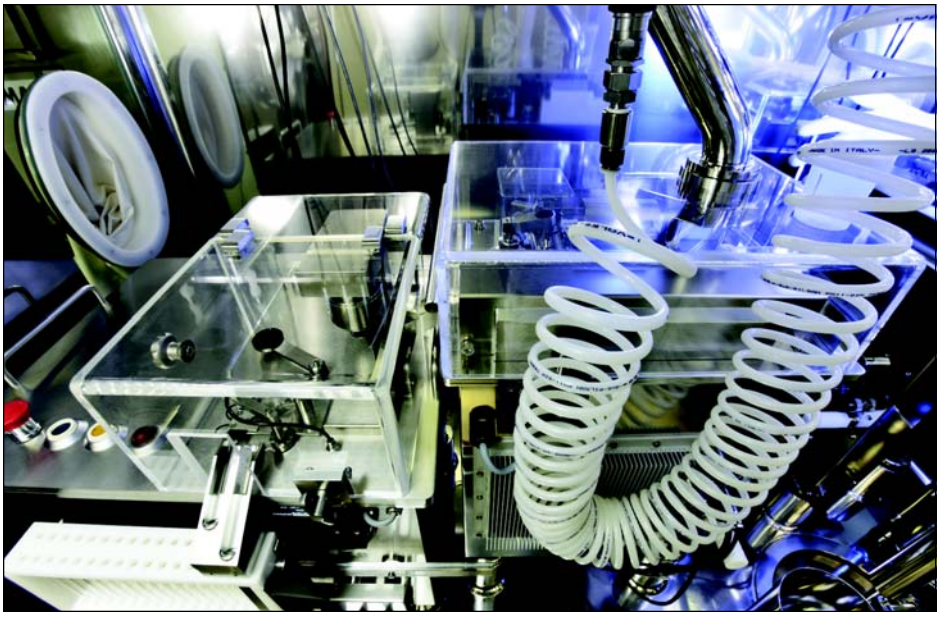
Improvements in PAT

Process Analytical Technology (PAT) applications also were improved upon with the goal of aggressively moving toward real-time release for the product. "We are very proud of the PAT improvements," said Bernhard.

In the mixing and granulation process, Near Infra-Red (NIR) spectroscopy is used to check whether the mixture is homogeneous and the active substance is present in equal doses in all the tablets. Not only is the data used to verify the quality of the product, but it has the potential to shorten blending cycles.

For the tablet press, a special device was developed to extract coarse directly from the press in order to measure tablet

Concludes on page 8.



PAT technology.

Compression operation (incl. PAT application).

potency. The vision is for this continuous online analysis to replace the time consuming, manual HPLC testing in the future, and to allow staff to respond swiftly in the event of faults or irregularities. Pfizer Illertissen is currently gathering data and plans to file this PAT application with the authorities by the end of this year, Weyhers said.

Lean Concepts Optimize Throughput

The concepts of lean manufacturing also were applied to identify bottlenecking and potential improvements. With model simulation software, NEWCON production processes were illustrated virtually and optimized.

"We wanted to achieve line balance, meaning the focus is to equally load the major unit operations of compounding, core compression, and film coating," said Weyhers. "Our findings had an impact on equipment size and selection, and this was done up front."

The NEWCON team of experts was able to achieve synchronized unit operations. As soon as the first process stage is completed, the next batch is brought in, so that up to three batches can be produced in parallel. This semi-continuous production sequence has resulted in a significant increase in output compared with ICON. NEWCON has a capacity of a billion tablets per year in three-shift operations round the clock and five days a week.

With the implementation of principles of lean manufacturing, Bernhard said they were able to reduce the operator level by 66 percent, which corresponds to an increase in efficiency of 300 percent. Together, with an increase in the batch size, there also was a reduction in the production costs by 42 percent, compared with ICON.

Streamlining C&Q

The philosophy of improving and streamlining NEWCON's design also was applied to NEWCON's Commissioning and Qualification (C&Q) approach.

"If we used the conventional approach of 'the more the better,' we simply would have missed the timeline. We had to come up with something different," said Weyhers.

"We have a saying within Pfizer Global Manufacturing: Shamelessly steal good ideas. We simply made use of the ISPE GAMP® 4 Guide."

"Based on risk assessment, we categorized our systems into Direct, Impact, and Non-Impact systems and this really helped to funnel down the overall validation approach and unburden the organization," said Weyhers. "We managed to shift the major chunk of the workload toward the vendors."

"At the end of the day, it's the product that counts," said Bernhard. "The equipment and facility serve one purpose, and that's to produce a good, safe, quality product for the patient. We focused on what was important, and I'm happy that this logical approach is becoming more and more prevalent in the industry."

Crazy Can Lead to Pioneering

The vision for NEWCON started a few years ago with a team of experts asking crazy questions and answering with 'why not?' said Bernhard.

Today NEWCON provides pioneering ideas for the future, not only in containment production, but for the entire field of pharmaceutical manufacturing, said Bernhard.

"It is certainly plausible that the degree of automation that Pfizer Illertissen has achieved in NEWCON will be standard for the pharmaceutical sector in one or two decades," said Bernhard. "And it is just as likely that the fully-automated containment technology will then be used not only for highly potent substances, but also in other areas of pharmaceutical manufacturing. For example, perhaps the single-room concept can be applied to a packaging line."

"These days, with cost pressures, decreasing direct labor costs, and market challenges, automation should be considered in facility design in order to be competitive in this industry."

BELIVE IT OR NOT, FINALLY WE ARE IN GOOD HANDS

The right partner in Isolator Technology

COMECER®
SAFETY FIRST

For more than 40 years one of the leading companies in the Isolator Technology industry, from stainless steel to IQ/OQ, COMECER always delivers the best solutions

- Customized solutions and flexible approach
- Integration of a variety of different pharmaceutical processing machinery and equipment for large or small production, R&D applications, highly active compound processing and aseptic production, quality control and sterility test
- Turn key solutions: from project evaluation and design qualification to IQ/OQ and post sales service are performed exclusively by Comecer trained personnel
- Advanced construction methods and ergonomic studies ensure excellent cleaning cycles, durability and ease of use
- Certified total quality management system

2008
Facility of the Year Awards
CATEGORY WINNER
Process Innovation • Supplier

Congratulations to Pfizer: we are proud to be the isolator supplier for the center of excellence in containment manufacturing in Illertissen, Germany

COMECER Inc.
SALES & CUSTOMER CARE • TECHNICAL SUPPORT • POST SALES SERVICE
429 Lenox Avenue - Miami Beach, FL 33139
Phone: 1-(305) 673-6020 Fax 1-(305) 847-0837
E-mail: info@comecerinc.com

Comecer representatives will be at the ISPE Annual Meeting in Boca Raton, Florida, 26-29 October, Table #623

COMECER S.p.A. Via Emilia Ponente, 390-48014 Castel Bolognese (RA) Italy
Tel. +39-0546656375 Fax +39-0546656353 E-mail: comecer@comecer.com

100% MADE IN ITALY

www.comecer.com

Category Winner – Facility Integration

Boehringer Ingelheim

To accommodate a growing number of development projects and to promote the application of new technologies, Boehringer Ingelheim (BI) erected the new Pharmaceutical R&D Building in Biberach, Germany.

This state-of-the-art facility integrates all major functions of pharmaceutical development – formulation, process development/scale-up, clinical supplies manufacture, and packaging/labeling – in one building.

The Value of Synergy

BI's key goal is to bring value to patients by researching and developing innovative pharmaceutical medicines. The Biberach site represents not only the largest of BI's R&D centers within the global network of interlinked R&D facilities, it also is their global center for research in the areas of central nervous diseases, metabolic diseases, respiratory diseases, and a key global skill center for development.

The existing premises for pharmaceutical development at the Biberach site had been distributed in several buildings and needed substantial upgrading, including additional laboratory space.

In 2002, a planning process resulted in the decision to create a new building that should house all relevant disciplines of pharmaceutical development, providing a basis for the optimal exploitation of synergies between all functions.

Exterior view of the pharmaceutical R&D building.

Different but Related

Pharmaceutical development of drug products encompasses several disciplines, which are functionally related, but require different prerequisites that were reflected in the facility design, including:

- *Formulation development* uses laboratories for small-scale experiments to develop preliminary formulations with new compounds for first clinical trials and subsequently design formulations for the market use.
- *Process development/scale-up* requires pilot plant facilities equipped with all machinery necessary to develop and optimize manufacturing processes ready for transfer to commercial production.
- The manufacture of *clinical trial supplies* requires adequate space and equipment in full compliance with all international GMP requirements.
- To support international clinical trial programs, a globally organized unit for the coordination of all BI clinical trials, including GMP packaging/labeling operations is to be integrated.

GMP Standards for Diverse Products

One of the major goals of the project was the

Boehringer Ingelheim

Category Winner – Facility Integration

Project: Pharmaceutical R&D Building Biberach
Location: Biberach, Germany
Project Management: Boehringer Ingelheim Pharma GmbH & Co. KG
Architect: Henn Architekten
Domestic Engineering: Ingenieurbüro Mayer
General Contractor: Axima GmbH
Size: 95,357 sq. ft. (8,859 sq. m.)
Cost: US $64.7 million (46 million Euros)
Product: Clinical trial supplies phase I – IV for oral solids and liquids, sterile drugs/parenterals, highly potent compounds
Key Project Participants:

ECOS	Rieber	Stotz GmbH
Lohr GmbH	Starksstrom Systeme GmbH	Waldner
Repass GmbH		

creation of state-of-the-art GMP facilities for the manufacture of solid, liquid, and parenteral clinical trial supplies. All relevant international GMP standards had to be met. Since all clinical trial phases from I to IV had to be supported, multi-purpose facilities and equipment were made available for manufacturing operations with batch sizes from one up to approximately 200 kg, depending both on the availability of drug substance and the trial size.

"Since the pilot plants are operated under full GMP, process development and subsequent clinical trial supplies manufacture can occur in the same premises, without additional technology transfer," said Dr. Manfred Fiebig of Boehringer Ingelheim R&D.

Important features of the applied GMP concept within the facilities are:

- zoning concepts for all three GMP facilities (solids manufacture, sterile area, packaging/labeling) with airlocks providing a clear separation from the non-GMP area, supported by building design and technical control systems
- processing rooms with adjacent technical areas and accessible cleanroom ceilings for technical installation above, allowing maintenance without disturbing the process flow
- corridors function as a buffer area, guaranteeing ideal room conditions within the processing rooms

Handling Highly Active Compounds in a Development Environment

A challenging task for the project team was the creation of areas for safe handling of highly potent actives without compromising the flexibility necessary in a development environment.

"The creation of safe handling of highly potent actives without compromising flexibility represents a strategic advantage in a field where a trend to higher potent compounds can be observed," said Fiebig.

The solution derived from a longer planning and testing phase and resulted in a two-way approach for the new building:

- For larger scale operations, special HVAC systems were developed, which lead to a significant reduction of dust exposure by technical means in the pilot plant, providing the option to handle highly potent compounds down to OELs of approx. 10 µg/m³ ('SMP area').
- Two separate isolator suites for handling highly potent compounds (OEL > 0.1 µg/m³) were installed, capable of GMP manufacture and development work in small scale.

Isolators and equipment are operated under GMP conditions and are suitable for formulation development and manufacturing of small-scale clinical trial supplies.

The introduction of downflow booth technology combined with a sophisticated HVAC system in the pilot plants extends the range of workable compounds down to OELs of approx. 10 µg/m³, without compromising safety at work or process flexibility. Filter units are designed for dust-free maintenance and exchange; all processing rooms are monitored with pressure and overflow controls.

Notes from the Judging Panel – What Impressed Them

This building project achieved the integration of all major pharmaceutical development functions into one building without disruption of ongoing operations. Flexibility across a broad variety of processes and batch sizes is achieved through the use of building layout and zoning concepts that include open production areas. Areas for handling potent compounds also were created without compromising the flexibility necessary for development activities. Throughout the project there was a focus on promoting synergies necessary to execute effective product and process development work.

Column-free areas support flexible use of rooms and equipment.

HVAC system.

Category Winner – Equipment Innovation

Bristol-Myers Squibb

Forecasting a 20-year business plan, Bristol-Myers Squibb (BMS) developed and implemented a new strategy to discover and develop innovative medicines to address significant areas of unmet medical needs. These areas include affective (psychiatric) disorders, Alzheimer's/dementia, atherosclerosis/thrombosis, diabetes, hepatitis, HIV/AIDS, obesity, oncology, rheumatoid arthritis, and related diseases as well as solid organ transplant.

BMS CSO/DPTC facility.

Bristol-Myers Squibb

Category Winner – Equipment Innovation

Project: Clinical Supplies Manufacturing and Drug Product Technology Center Expansion
Location: New Brunswick, New Jersey, US
Engineering/Design: IPS, Inc.
Construction Manager: Torcon, Inc.
Size: Phase One 93,110 sq. ft. (8,650 sq. m.); Phase Two 39,300 sq. ft. (3,651 sq. m.)
Cost: Phase One US $53,719,000 (38 million Euros); Phase Two US $36,968,000 (26 million Euros)
Product: Solid and liquid dosage forms, including sterile products
Key Project Participants:

Air & Electric Equipment
Air & Specialities
American Leistritz Extruder
Avon Drywall Contractors
BOC Edwards
Buffalo Air Handling
Carlisle Life Sciences (CPS Barrier)
Carrier
Crisdel
Dancker, Sellew, and Douglas Commercial Interiors
Donald C. Rodner, Inc.
Fine Painting
Foley Power Systems
Fromkin Brothers
GQS Innovation, Inc. (VAI Automation, Inc.)
Groninger
Independent Balancing/Air Balancing Engineers, Inc.
Independent Sheet Metal, Inc.
Integrity Piping Solutions
K.B.I.
Kinetic Systems
Kosson Glass
L.B. Bohle
LCS, Inc.
Long Island Fire Doors
McGiver Spray Systems
Munters Corporation/ Industrial Dehumidification Div.
Niro, Inc.
Omni Instrumentation
Papp Iron Work
Penntech Machinery Corp.
PMDI Architectural Signage
Pyromax, Inc.
Quick Response
R. Baker & Son
Servolift LLC
Siemens Building Technologies
Skan AG
S.M. Electric
SP Industries
Steris Corp.
Thermal Product Solutions
Thyssen Krupp
VAL Floors

To further develop its product pipeline, foster collaboration among numerous functions and facilities, and sustain on-time delivery of future clinical supplies, BMS designated its New Brunswick, New Jersey, US campus as a Pharmaceutical Development Center of Excellence. To create this Center, BMS embarked on its Clinical Supplies Manufacturing and Drug Product Technology Expansion Project.

Striving for Excellence in Clinical Supplies Manufacturing

The production of clinical supplies involves added complexity in comparison to marketed products by virtue of the lack of fixed routines, variety of clinical trial designs, complex packaging designs, and the increased risk of cross-contamination. The complexity of the project was increased with the integration of innovative isolation technology.

The project brought early and late phase cGMP clinical manufacturing and development scale-up together a single facility to create a Pharmaceutical Development Center of Excellence. Construction of the project was phased to allow full implementation of lessons learned in containment, and process automation technology was integrated into already existing operations.

Compressing the Critical Path

Phase One of the project implemented a state-of-the-art Clinical Supply Operations

Continued on page 14.

Congratulations Bristol-Myers Squibb,

Category Winner, Equipment Innovation, 2008 Facility of the Year Award.

"Complex and challenging projects demand the best people who have experience with specific technology AND have the ability to see the whole picture. Our integrated approach to facilities means that you get critical perspectives, on every project, from our entire team."

ips

Talk with our Experts about the strategic solutions to reach your business goals. Contact **Kimberly Goodman at 888.366.7660** or visit

www.ipsdb.com

Knowledge Delivered

Cover Image: Amy Shutt, PE, LEED® AP, Senior Mechanical Engineer, IPS

"The goal was to create a flexible facility capable of performing multi-product clinical scale manufacturing and processing solvent-based and potent compound operations."

(CSO) expansion facility, including full containment for expanded Oral Solid Dose (OSD) operations, and according to a BMS spokesperson, the most flexible clinical-scale continuous barrier line in the US for sterile products. This facility was designated for manufacturing OSD batches up to 400 Kg and parenteral liquid fill batches up to 250L. The goal was to create a flexible facility capable of performing multi-product clinical scale manufacturing and processing solvent-based and potent compound operations.

Phase Two built upon the technologies in Phase One and added additional processing space to the OSD clinical operation and a new stand-alone Product Technology Center (PTC) for development scale-up activities. The addition to OSD operations allows the manufacture of long term stability batches within the CSO facility in at least one-tenth commercial scale.

Innovation in Isolation Technology

The Phase One expansion was segregated into three manufacturing zones: Parenteral, OSD Band 1 through 4, and OSD Band 5.

The CSO Parenteral area is equipped with an isolated vial filling line to satisfy both sterility and containment requirements. Features of the filling line include:

- manufacture in a full nitrogen environment for safe solvent processing
- manufacturing of a full range of vial sizes
- filling technology that utilizes peristaltic or rotary piston pumps
- automatic loading of the freeze-dryer with no trays or rings that can alter heat transfer between the shelf and the vials
- standard and cold-shelf loading of the freeze dryer

Isolated tablet press.

Concludes on page 16.

GEA

Innovative solid
dosage technology

Congratulations to Bristol-Myers Squibb it was great working with you

Winners of the ISPE 2008 Facility of the Year Award for Equipment Innovation.

The demand for innovation in pharmaceutical manufacturing grows every year – and as active ingredients become increasingly powerful and expensive, so does the need for effective containment and cost control. The Bristol-Myers Squibb Clinical Supplies Manufacturing & Drug Product Technology Center in New Jersey is a model of world-class manufacturing technology. Good environmental design…easy cleaning…high productivity…top quality…true innovation. We are proud to have been part of the team. It was great working with you.

**Innovation with teamwork –
an unstoppable combination**

2008
Facility of the Year Awards
CATEGORY WINNER
Equipment Innovation • Supplier

GEA Pharma Systems

GEA Process Engineering Inc., 9165 Rumsey Road, Columbia, MD 21045
Tel: 410-997-8700 • Email: info@niroinc.com

www.geapharmasystems.com

Integrated contained high shear granulator and fluid bed processor.

Isolated single pot process with dryer and isolated automated sampler.

- use of product thermocouples within the isolated environment
- capping under full Grade A/Class 100 conditions
- automated differential pressure control scheme to maintain containment of potent compounds
- exterior vial wash capability to remove any product residues

The OSD Band 4 Manufacturing Area includes processing rooms focused on the production of oral solid dosage clinical materials. The area was designed for operations handling Active Pharmaceutical Ingredients (APIs) categorized as Band 4 and below. The OSD Band 4 area was expanded in Phase II to include the Long Term Stability (LTS) area. The LTS area includes processing rooms focusing on the production of oral solid dosage clinical materials and handling API categorized as Band 4 and below and also includes one room capable of handling solvent coating of up to Band 5 compounds. The manufacturing of LTS batches aids product scale-up and technical transfer into commercial manufacturing sites with batch sizes at least one-tenth commercial scale.

The OSD Band 5 area is used for OSD operations handling APIs categorized as Band 5 and includes two processing suites.

Primary equipment containment utilizes several isolation/containment technologies, including closed system processing equipment, contained material transfer systems, and isolated equipment and operations. The two OSD processing suites support a variety of contained OSD operations, such as wet and dry granulation, bin tumble blending, compression, encapsulation, tray drying, and dry milling.

"Phase Two of the project was designed to build upon the innovation in Phase One and add supplemental processing space and scale to the oral solid dose clinical operation."

More Space for More Innovation

Phase Two of the project was designed to build upon the innovation in Phase One and add supplemental processing space and scale to the oral solid dose clinical operation. Additionally, a new Product Technology Center focuses on R&D and scale-up for future CSO technologies.

The PTC area is designated to perform both process development and scale-up. Batch sizes for the PTC range from 20Kg to 100Kg and are manufactured using different unit operations and processes. Although the operations performed within the PTC area are characterized as non-GMP activities, the qualification, maintenance, and operation strategies provide sufficient support for future changeover to cGMP operations. In addition, the area is designed for operations handling API categorized as Band 1 through 4.

Notes from the Judging Panel – What Impressed Them

This project implemented a unique combination of innovative isolator technology on existing equipment used in the manufacture of clinical supplies. Multiple filling technologies also are implemented, including clinical scale autoloading of lyophilizers. The project also implemented unique automation techniques involving the retrofitting of wireless transmitters onto existing equipment.

CONGRATULATIONS BRISTOL-MYERS SQUIBB, CATEGORY WINNER, EQUIPMENT INNOVATION, 2008 FACILITY OF THE YEAR AWARD.

2008 Facility of the Year Awards CATEGORY WINNER Equipment Innovation

WE ARE HONORED TO HAVE BEEN THE MAJOR SUPPLIER OF THE ISOLATORS FOR THE FILL-FINISH AND OSD OPERATIONS FOR YOUR FACILITY

SKAN US Inc, • 2655 Industrial Lane • Broomfield, CO 80020 • Phone +1 866 381 7685 • info@us.skan.ch

Category Winner – Operational Excellence

IDT Biologika GmbH

Innovative and promising vaccines to fight major global diseases and new technologies enabling efficient production of those vaccines are market drivers that led IDT Biologika to build the facility for the production of Live Human Viral Vaccines, IDT 201 in Dessau-Rosslau, Germany.

IDT used the latest technologies in sterile production and operational expertise gained from more than 10 years of contract manufacturing experience to design the facility.

Exterior view on the west side of the new facility.

Frontloading Solutions

The project expands IDT's Dessau site from one to two buildings for vaccine production. The new building includes two different aseptic production lines for egg-based and cell culture production and implements Restricted Access Barrier Systems (RABS) and robotic systems to maximize flexibility and improve production efficiency.

The expansion allows IDT's capacities to produce viral vectors from process development through Phase 1 and 2 clinical trials and up to manufacture of batches for Phase 3 testing, and subsequent commercial production. IDT's new facility is one of a few in Germany and worldwide that has the capacity for large-scale, campaign manufacture of batches of different vaccine products.

Constructed within 19 months and operating since the end of 2007, the project involved several new and prototype solutions, posing major challenges in implementation and operation, said IDT officials.

"But these were resolved by extraordinarily cooperative planning and design by IDT and its infrastructure unit's subcontractors in the design and prototyping phase, thus frontloading all problem resolutions and excluding expensive failures after implementation," said IDT officials. "Extensive prototype modeling and testing had been done."

IDT Biologika GmbH

Category Winner – Operational Excellence

Project: Facility for Production of Live Human Viral Vaccines, IDT 201
Location: Dessau-Rosslau, Germany
Architect/Designer: Heene + Proebst GmbH
Process Engineering: BIDECO GmbH
General Contractor: Technik-Energie-Wasser Servicegesellschaft mbH
Size: 50,568 sq. ft. (4,698 sq. m.)
Cost: US $37,470,000 (26 million Euros)
Products: Live recombinant and non recombinant viral vaccines for human use
Key Project Participants:

AAR	Mayer Ing. Büro für TGA	TIRA
BELIMED	Neuberger Gebäudeautomation	Waldner Anlagenbau
EHRET Labor-u.Pharmatechnik	The Automation Partnership LTD	WAVE Biotech AG
Franz Ziel GmbH		ZETA
Laservorm GmbH		

Sterility Does Not Have to be Lifeless

The building's colorfulness and transparency signal new ways of designing sterile production work environments. Sterility does not have to be lifeless, according to IDT representatives.

Cleanrooms with glass walls, material locks with glass doors, and glassed-in passageways for flat surfaces, allow complete visibility, and meet the most rigorous standards for cleanliness. Trust in personnel and product is inspired through openness and transparency.

Combining Technology and Operational Expertise

The multi-purpose facility consists of strict horizontal division of service areas and the serviced areas into four levels. A strategy

was devised to guarantee the shortest supply and disposal routes: the production area is located at the building's center with maintenance level and air conditioning systems located above and the media supply for the production area below. All operations are as much as possible contained in cleanrooms and contained technical systems.

Roller culture used for virus production has been fully automated in Class A (100) cleanrooms using robots.

Two production lines were created for different aseptic manufacturing technologies with a fumigation lock, automated laser technique for opening eggs, and Restricted Access Barrier System (RABS) for processing eggs on one line. The other line has robots for cell culturing and virus propagation. The production area also includes a second cooling system for -80°C storage, fully automated CIP/SIP, and continual wastewater inactivation.

Large cleanrooms classified B (10,000) and C (100,000) allow long-term space for climate chambers of every temperature range making virus production on various cell substrates and different technologies possible.

Since the vaccines currently being manufactured are live virus vaccines which cannot be sterile filtered, the use of optimal aseptic production technologies was critical. These technologies include an automatic disinfection hose for eggs, a laser for opening the eggs, a RABS for extracting the embryos, and the use of a hose-sealing system for creating all hose connections during production. The use of these technologies achieves a closed process for the entire chain of production steps.

Building in Efficiency and Flexibility

With the ability to fumigate all production rooms with formalin, it is possible to change production campaigns on each production line within 12 hours. Since the separate production rooms are fully independent from one another, it is also possible to facilitate a campaign switch step by step, room by room (from USP to DSP).

Through the use of robots to process roller bottles, the personnel required for this step was reduced by half and at the same time a higher production safety could be guaranteed through improved aseptic production conditions.

Equipping the rooms with standard media panels supplying all available media and mobile hanging media panels capable of being adjusted into nearly every position in each of the cleanrooms, makes it possible to introduce new equipment at any time and significantly increase production capacity.

Highest Level of Containment

Access to the building, various production areas, and cleanrooms is controlled by an electronic access system. All handling of open virus material occurs under at least Class II safety workbenches. Using robots during production of infectious material in sub-pressure conditions fulfills the highest level of containment, thus protecting employees from infection. Deviations from target values are signaled on internal and external monitors. Connecting, disconnecting, and sealing hoses are done at high temperature with hose-sealing devices. Eye washes in sterile disposable bottles are, in an emergency, better alternatives than conventional systems.

Notes from the Judging Panel – What Impressed Them

Using experience over 10 years of production of viral vaccines as a design tool, this project's use of unique transparent building features, manufacturing area adjacencies, material handling, and equipment technologies is anticipated to result in a four-fold increase in production capacity. Two different aseptic production lines for egg-based and cell-culture production implement RABS and robotic systems to maximize flexibility and improve production efficiency.

Cell and virus propagation in disposable fermentor systems.

Flexible docking station for utilities and waste water.

Category Winner – Project Execution

F. Hoffman La Roche AG

To make their innovative cancer drugs available as quickly as possible to an increasing number of patients, Roche initiated expansion of its Penzberg, Germany site.

The expansion project, called "Biologics IV," increases production capacity for Trastuzumab, the Active Pharmaceutical Ingredient (API) for the anti-breast cancer drug Herceptin®. An "ultra fast track" project execution strategy resulted in delivering a large, technically complex project ahead of schedule, under budget, and to the complete satisfaction of the user.

A Compelling Motivation

Headquartered in Basel, Switzerland, Roche is one of the world's leading research-focused healthcare groups in the fields of pharmaceuticals and diagnostics. The company is a world leader in in-vitro diagnostics and drugs for cancer and transplantation, a market leader in virology, and active in other major therapeutic areas such as autoimmune diseases, inflammation, metabolic disorders, and diseases of the central nervous system.

To make their innovative biotechnologically produced cancer drugs available to an increasing number of patients, a phased expansion of Roche's Biologics capacity was initiated. This involved several major projects in the Roche group, including Biologics IV.

Biologics IV office and laboratory building.

The scope of Biologics IV includes a four-story high building containing two highly automated, recipe controlled production lines, each centered on three 12,500 Liter fermenters and downstream processing. The project also included associated laboratory and office space.

Biologics IV achieved its first production batch just 36 months after the start of conceptual design. Once running at full capacity, Biologics IV will enable supply for 100,000 additional Herceptin patients per year.

Project team members largely credit their success to innovative and effective project execution strategies and integrated teamwork.

High Performance Project Organization

"Leadership and organization, besides all the technical aspects, is very crucial for a project like this," said Project Director Claus Herrmann.

Setting up a high performance project organization includes several key planning practices, including identifying and prioritizing key stakeholders, said Herrmann. "If stakeholders are popping up down the road, that's not a good thing because they come up with some new requirements."

Another practice is securing the best available resources and giving them clearly defined roles and responsibilities. "You need leaders, including your general planner, construction management, suppliers, and

F. Hoffmann La Roche AG

Category Winner – Project Execution

Project: Biologics IV
Location: Penzberg, Germany
Architect: Koppenhöfer & Partner GmbH
Engineer: Roche Pharma Global Engineering
Engineering Contractor: LSMW GmbH – Total Life Science Solutions
Construction Manager: SIBC GmbH – A Turner & Townsend Co.
Size: 355,209 sq. ft. (33,000 sq. m.)
Cost: US $460 million (327 million Euros)
Product: Trastuzumab (API for Herceptin®)
Key Project Participants:

Alfa Laval	Kardex	Siemens
Bolz	Lang & Peitler	Stadler + Schaaf
Binder	MCE	Stedim
Chemgineering	Millipore	Val-It
Christ	Pall	Vogelbusch
Endress & Hauser	Pharmatec	VTU
GEA-Diesel	Sartorius	Waldner
Gemü	Schindler	Zeta
Imtech		

automation contractor, with strong leadership capabilities," said Herrmann. "Without strong leaders a project like this tends to be uncontrollable."

Herrmann offers three top tips when it comes to setting up a high performance project organization:

- **Share your compelling vision and strategies.**

"In our case, it was to make this drug available for patients," said Herrmann.

- **Get the Users on board from day one.**

"If they come in toward the end of the project and tell you what they really need, that causes change orders you can avoid had they been involved from the very beginning," said Herrmann.

The Users, led by Dr. Juergen Wahl, head of Biotech Production Penzberg, were key team members. The Users were fully integrated into the project team from day one and took part in every aspect of the project, resulting in the Users receiving a facility in which they were fully trained, leaving them free to focus on production.

- **Proactively manage information flows.**

"In a large and complex project like this, we spent about one million man hours on engineering and automation," said Herrmann. "You have to coordinate all these disciplines and make sure everybody is working toward the same goals. This requires a lot of information flow and that doesn't flow by itself. You have to catalyze it."

The project team invested a great deal of time and effort to ensure the contractors were fully integrated into the spirit of the project. Team building workshops and social events to celebrate success were a welcome feature of the project. Challenges were openly discussed with the contractors in a "no blame" culture with suggestions welcomed, evaluated, and acted upon.

Starting in project initiation and continuing through qualification, Herrmann organized a series of workshops where the challenges, risks, and solutions were systematically identified, analyzed, and resolved. The critical series of workshops devel-

Concludes on page 21.

Notes from the Judging Panel – What Impressed Them

This multi-building example of ultra fast track project execution achieved its first production batch 36 months after the start of conceptual design. The final project cost was below budget and resulted in high satisfaction ratings from the owner. The turnover of the manufacturing facility was accomplished three months ahead of the original schedule and the turnover of the production line for monoclonal antibodies was completed four months ahead of schedule.

Fermentation area with glass facade.

oped the highly successful and innovative execution strategies for design, procurement, construction, and commissioning.

The complete Penzberg team developed a close cooperative relationship with their Roche colleagues who were simultaneously constructing a new biotech production facility in Basel, Switzerland. The exchange of knowledge and experience was highly valued by both teams. This led directly to cost and time savings when solutions to common problems were implemented on both projects.

Time and Cost Saving Strategies

A schedule analysis showed that the equipment and piping installation and automation software development drove the critical path during construction.

Building on experience of past projects, the team realized that skid mounted equipment reduced process equipment installation time from weeks to days. "We constantly strive to reduce our capital costs," said Herrmann. "A major factor in our success is not 'reinventing' solutions to known problems. The use of skid mounted equipment is a tried and tested solution in Roche."

The project team also focused its attention on automation. Borrowing software techniques from the telecom industry, the huge volume of process automation software was broken down into small modules and additional programming resource was applied to compress the writing and testing time.

The final compression of the schedule was achieved by analyzing the commissioning and qualification steps required. Everything possible was commissioned and qualified in the factory. The actual field commissioning and qualification was managed using "Petrochem Shut Down" techniques. The work was subdivided into small tasks and two seven-day week shifts were employed to reduce the commissioning/qualification time to a minimum.

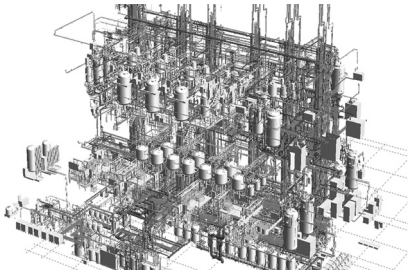
For the Cleaning and Sterilization in Place, which was critical to the success of the facility, the Users brought the practical knowledge from every day experience and the design engineers developed the system around the operative requirements. The resulting systems run efficiently.

The facility's Manufacturing Execution System (MES), including Electronic Batch Recording, was developed in a similar manner. The MES delivered a reduction of labor cost and an increase of production process quality.

Total Life Science Solutions

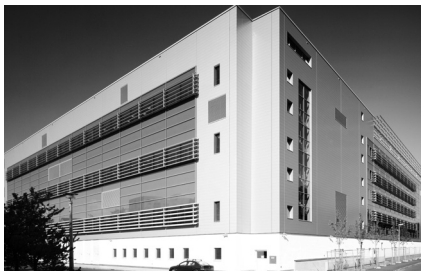
WE KNOW WHAT CHALLENGES ARE

CONSULTING ▪ ENGINEERING ▪ CONSTRUCTION
VALIDATION ▪ TECHNICAL FACILITY MANAGEMENT



CLIENT: Roche Diagnostics
LOCATION: Penzberg, Germany
PERIOD: 2004 - 2007
PROJECT: BIOLOGICS IV
New Biotechnological Production Facility with 2 Multi-Product Lines for the Production of Monoclonal Antibodies

“2008 Facility of the Year Category Winner”



CLIENT: GSK Biologicals
LOCATION: Dresden, Germany
PERIOD: 2005 - 2007
PROJECT: New Facility for the Production of Flu Vaccine

CLIENT: Hermes Pharma
LOCATION: Wolfsberg, Austria
PERIOD: 2007 - 2008
PROJECT: New Production Facility for Solid Dosage Forms

www.lsmw.com

LSMW IS PLANNER AND CONTRACTOR FOR LIFE SCIENCE & CHEMICAL INDUSTRY

GERMANY ▪ BERLIN ▪ BIBERACH ▪ FRANKFURT ▪ LEUNA ▪ LEVERKUSEN ▪ LUDWIGSHAFEN
NUREMBERG ▪ PENZBERG ▪ **STUTTGART** ▪ **AUSTRIA** ▪ LINZ ▪ VIENNA ▪ **SWITZERLAND**
BASEL ▪ ZURICH ▪ **POLAND** ▪ GDANSK ▪ WARSAW ▪ WROCLAW ▪ **THE NETHERLANDS** ▪ HELMOND

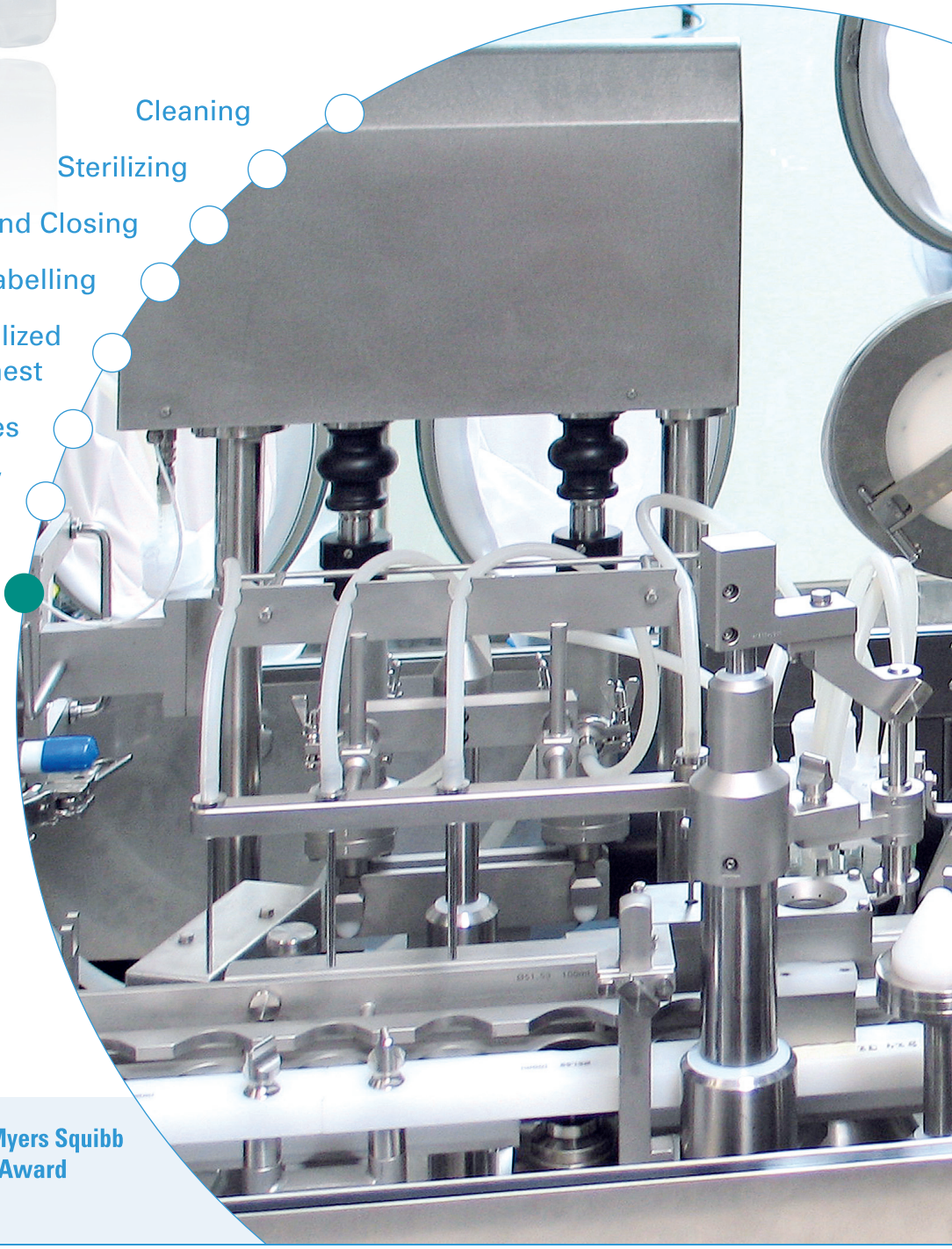
LSMW GmbH
Head Office
Lotterbergstr. 30
70499 Stuttgart
Germany
Phone: +49 711 8804-1800

germany@lsmw.com

groninger

Special machines for the pharmaceutical industry!

- Cleaning
- Sterilizing
- Filling and Closing
- Labelling
- Processing of presterilized syringes in nest
- Handling Devices
- Isolator technology / cRABS, oRABS
- Turn Key Solutions / Project Management



2008
Facility of the Year Awards
CATEGORY WINNER
Awarded by ISPE, INTERPHEX, Pharmaceutical Processing

We are proud to be a supplier of Bristol-Myers Squibb and congratulate on the Category Award „Facility of the Year".

@ **www.groningerusa.com**

groninger & co. gmbh · Hofäckerstr. 9 · 74564 Crailsheim · GERMANY · Tel.: +49 (0)7951/495-0 · Fax: +49 (0)7951/495-3138 · e-mail: office@groninger.de
groninger GmbH & Co. KG · Birkenbergstr. 1 · 91625 Schnelldorf · GERMANY · Tel.: +49 (0)7950/800-0 · Fax: +49 (0)7950/800-2123 · e-mail: office@groninger.de
groninger USA L.L.C. · 2520 Whitehall Park Drive · Suite 800 · Charlotte · NC 28273 · USA · Tel.: +1(704)295-9000 · Fax: +1(704)295-9020 · info@groningerusa.com