

Facility of the Year Special Edition

PHARMACEUTICAL ENGINEERING

THE OFFICIAL
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ISPE

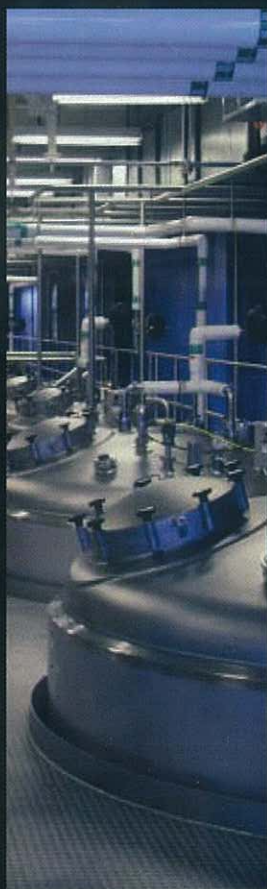
A Supplement to MAY/JUNE 2007



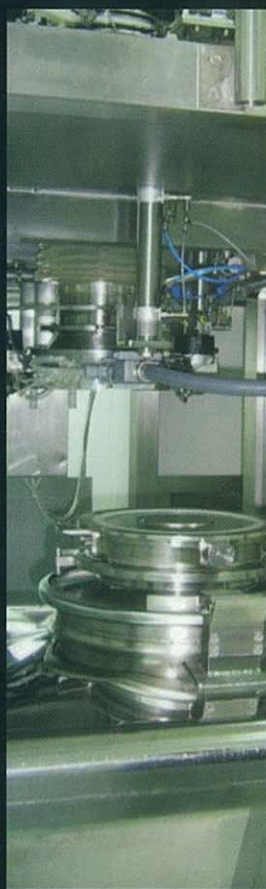
Facility of the Year Awards CATEGORY WINNERS



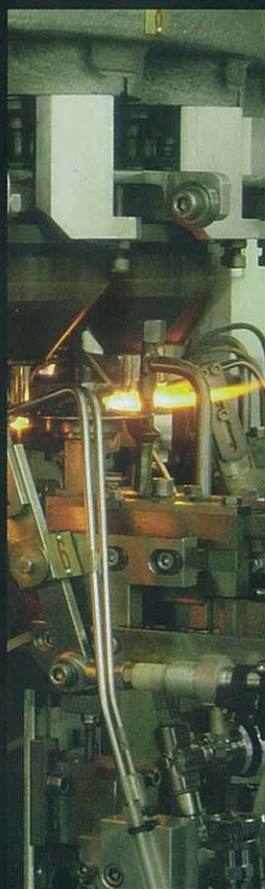
Facility
Integration



Project
Execution



Project
Execution
Regional
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Equipment
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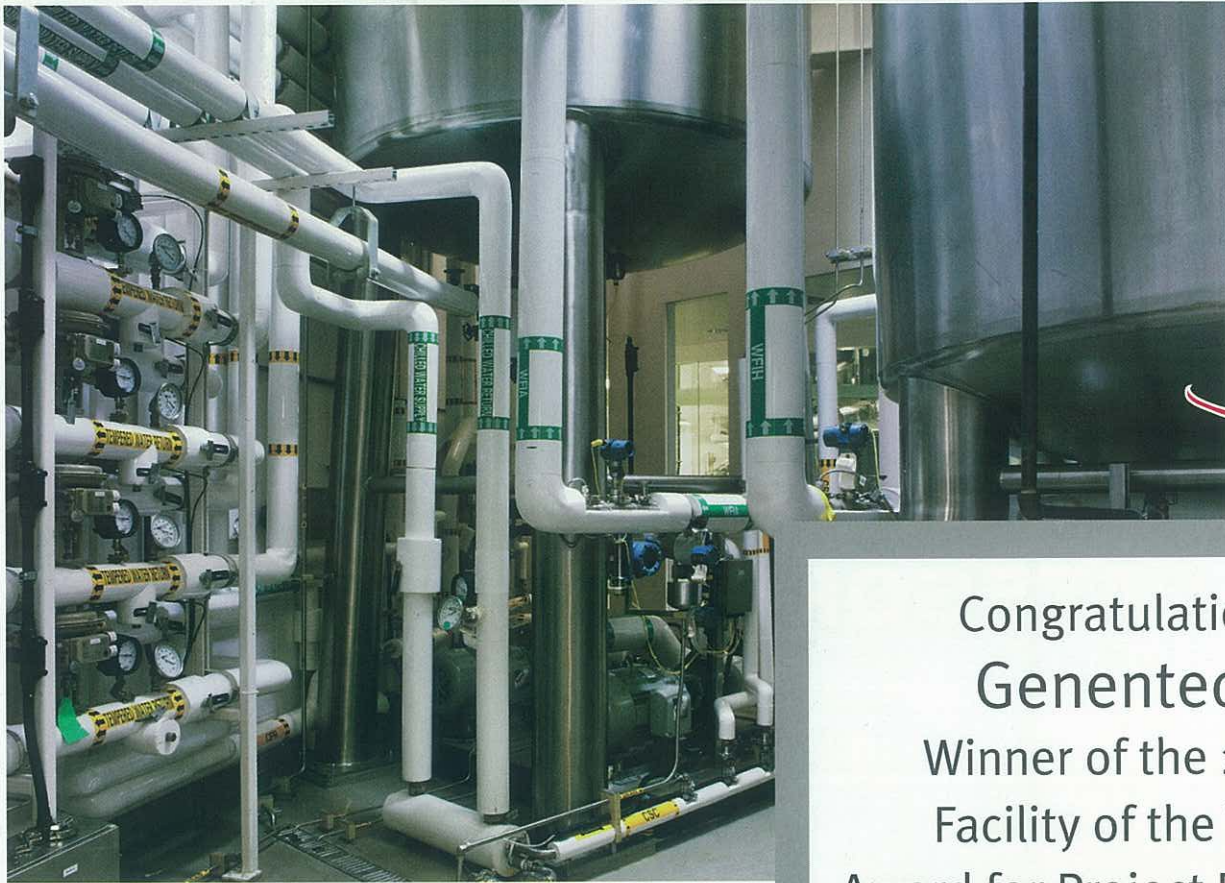


Process
Innovation

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Malaysia

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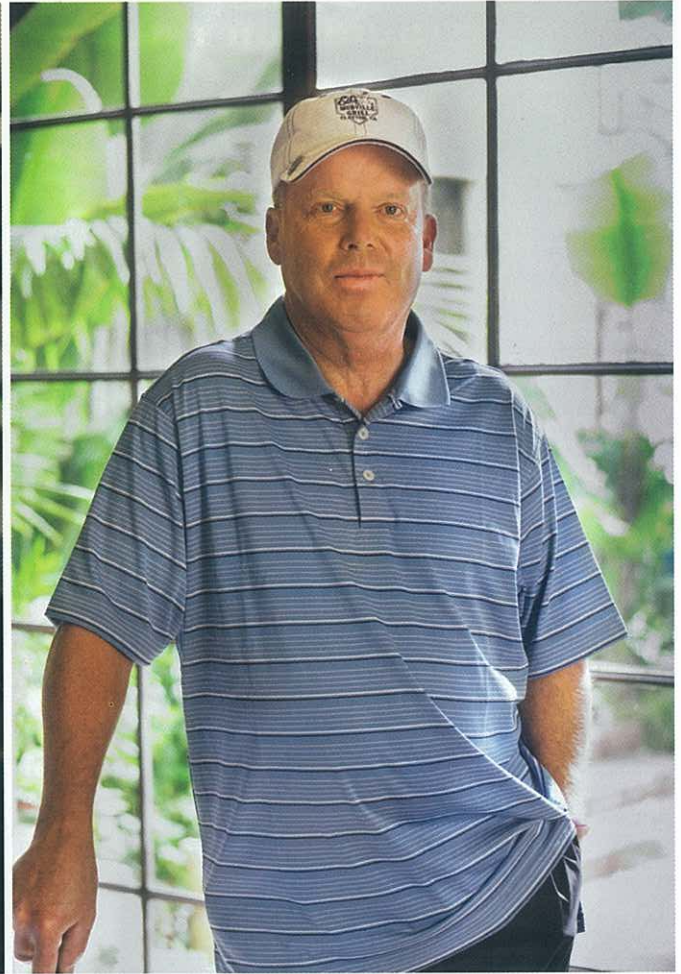


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Congratulations to our Oceanside facility for its Facility of the Year Award in Project Execution from the International Society for Pharmaceutical Engineering.

Genentech
IN BUSINESS FOR LIFE

Cover Photographs

Photos courtesy of Cook Pharmica LLC, Genentech, Shanghai Roche Pharmaceuticals Limited, Taiyo Pharmaceutical Industry Co., Ltd., and Vetter Pharma-Fertigung GmbH & Co. KG

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PHARMACEUTICAL
INNOVATION

Facility of the Year Special Edition

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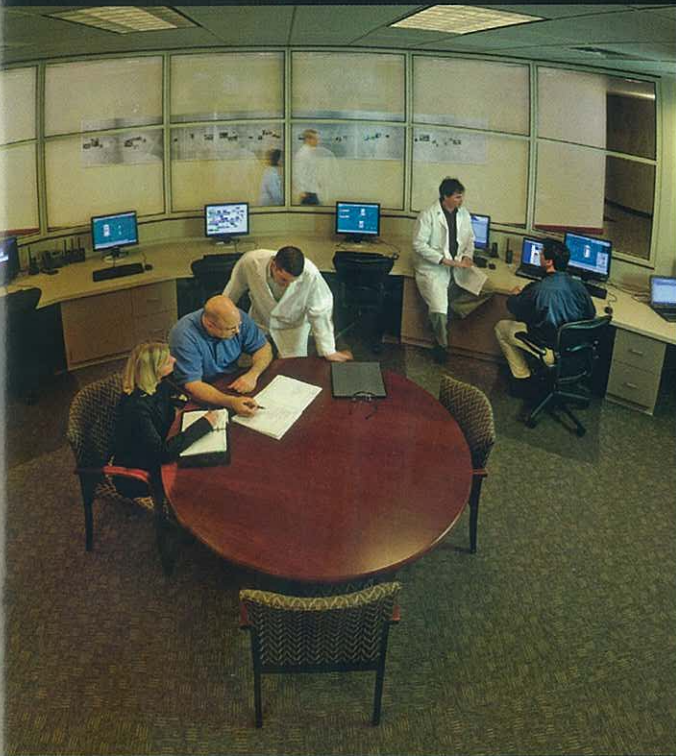
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2007
Facility of the Year Awards
CATEGORY WINNERS

CRB Congratulates Cook Pharmica

Winner of the Facility of the Year Award for Facility Integration Project Phoenix



Congratulations to Cook Pharmica for their foresight and commitment to the community to take an existing, abandoned manufacturing facility and turn it into a state-of-the-art biopharmaceutical manufacturing operation. CRB was proud to be a part of Project Phoenix and wishes Cook Pharmica continued success.

– Jeff Matis, CRB Project Manager



Project Facts

- 124,000 sq. ft.
- Project Cost: \$70,000,000
- Design Schedule: 6 months (concept thru final design)
- Construction Schedule: 10 months

Key Design Considerations

- Re-configurable commercial process and equipment focused on product characterization and scalability.
- Segregation of upstream and downstream operations as well as operations following viral inactivation and removal.
- Disposable technology selectively used with fixed equipment to reduce cleaning validation, contaminate risk and time for changeover.
- Viewing corridors and real-time web cameras allow visual accessibility to clients without compromising safety.



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The 2007 Facility of the Year Awards

The Facility of the Year Awards (FOYA) competition, 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 in its third year, the Awards program provides a platform for the pharmaceutical manufacturing industry to showcase its new products and accomplishments in facility design, construction, and operation, while sharing the development of new applications of technology and cutting-edge approaches that are being adopted by the industry.

The 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.

FOYA Program Enhancements

In an effort to properly acknowledge projects worthy of recognition, the sponsors made significant enhancements to the 2007 awards program. Awards are now given to leaders in specific categories, as well as the presentation of the overall Facility of the Year.

Submitting companies were asked to choose the category they applied for. Five Category Winners were selected based on:

- Facility Integration
- Project Execution
- Project Execution Regional Excellence
- Equipment Innovation
- Process Innovation

"The addition of Category Winners to the 2007 Awards program significantly improved the competition and effec-

tively enabled the judges to properly acknowledge those facilities that stood out and deserve special recognition," stated Andy Skibo, 2007 Judging Panel Chair, and Vice President Corporate Engineering and Capital Projects for Amgen.

"The Facility of the Year Awards competition 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."

Awards Recognition

Being named a Category Winner generates unsurpassed opportunities for the applicant manufacturer and those organizations that designed, constructed, validated, and equipped the facility to showcase their ingenuity in facility design.

Moreover, the competition offers an unprecedented opportunity for submitting companies, category winners, and the Facility of the Year Award winner to motivate colleagues within the industry toward these advances through the sharing of industry-wide best practices within the global community.

The announcement of the coveted overall Facility of the Year Award winner will take place at ISPE's 2007 Annual Meeting in November at Caesars Palace in Las Vegas. ISPE's Annual Meeting is the leading industry event attended by pharmaceutical manufacturing professionals. During the keynote session of this meeting, Category Winners will be introduced and formally recognized in front of their peers. Attendees will have the opportunity to speak with the Category Winners and learn more about the award-winning projects in the Facility of the Year Awards Display Area.

2007 Facility of the Year Awards Winners

Five pharmaceutical manufacturing facilities located in China, Germany, Japan, and the United States were selected as Category Winners. The companies and respective award categories include:

- **Cook Pharmica, LLC**, located in Bloomington, Indiana, USA, selected as winner of the Facility of the Year Award for Facility Integration
- **Genentech** located in Oceanside, California, USA, selected as winner of the Facility of the Year Award for Project Execution
- **Shanghai Roche Pharmaceuticals, Ltd.**, located in Shanghai, China, selected as winner of the Facility of the Year Award for Project Execution Regional Excellence
- **Taiyo Pharmaceutical Industry Co., Ltd.**, located in Takayama City, Japan, selected as winner of the Facility of the Year Award for Equipment Innovation
- **Vetter Pharma-Fertigung GmbH & Co. KG** located in Ravensburg, Germany, selected as winner of the Facility of the Year Award for Process Innovation

This Special Edition was developed specifically to highlight the remarkable features and technologies of each individual project. The following pages provide detailed case studies for each Category Winner project with emphasis on why they were deemed as "world class" by the 2007 Facility of the Year Awards Judging Panel, and more importantly, how their innovation and excellence are advancing the global pharmaceutical manufacturing industry.

Continued on page 30.

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Phoenix Soars to Great Heights in Facility Integration

The growing trend in cell culture-based therapeutics inspired Cook Medical to transform an abandoned television assembly plant into a cutting-edge contract manufacturing facility.

Aptly named after the mythical bird that rose above the ashes, Project Phoenix is the winner of the 2007 Facility of the Year Award (FOYA) for Facility Integration. The facility, located in Bloomington, Indiana, USA, is home to Cook Pharmica, a biopharmaceutical contract manufacturer of mammalian cell culture-based products.

The \$70 million, 124,000 sq. ft. build-out provides development services, flexible manufacturing, and analytical services to the global biotech community. With its two 2500L bioreactors, Cook Pharmica's current cGMP manufacturing and purification capacity is sized for clinical and small-scale commercial runs.

Among the many features that impressed members of the 2007 Facility of the Year Awards Judging Panel were the facility's highly advanced design, which incorporates disposable technologies, segregated production rooms, innovative wall pass-throughs and unidirectional flow of operators, equipment, and supplies to reduce the risk of contamination.

Entrepreneurial Spirit and Speculation

The business case for the facility was not based on a response to a contract with a customer; rather, on the intuitive, entrepreneurial spirit of Cook, as stated in the 2007 Facility of the Year Awards submission.

Considering the general awareness that research and

Cook Pharmica LLC

Category Winner – Facility Integration

Project: Project Phoenix

Location: Bloomington, Indiana, USA

Engineer: CRB Consulting Engineers, Inc.

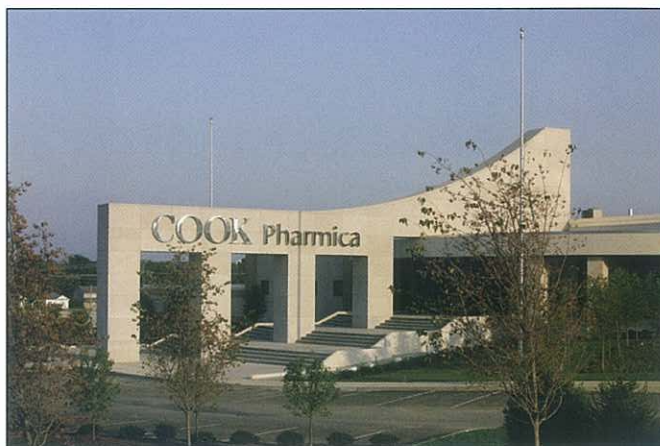
Construction Manager: R.L. Turner Corp.

Manufacturing Facility Design/Build: AES Clean Technology, Inc.

Size: 124,000 sq. ft. (11,520 sq. m.) build-out in a 450,000 sq. ft. (41,806 sq. m.) building

Cost: US \$70 million

Product: Mammalian cell culture-based production of API



Exterior view.

development of therapeutics was projected to heavily outpace that of small molecule products, Cook speculated that the need for API cell culture capacity would be in great demand by the time it was brought to market.

And, with an anticipated 47% of biopharmaceutical companies projected to outsource manufacturing operations by 2008 (*BioProcess International*, September 2006), Contract Manufacturing Operations (CMOs) were becoming an ever-increasing strategic initiative for the industry.

Recognizing these factors, Cook Medical, the largest privately held medical device manufacturer in the world, launched in 2004 its own biopharmaceutical contract manufacturing organization, Cook Pharmica, and shortly thereafter, Project Phoenix.

Making Room for a Different Technology

Cook searched the globe for the right location for Cook Pharmica, finally deciding on a site that was the former home of the world's largest television assembly plant. In 1998, and after more than 40 years of ownership, Thomson Consumer Electronics relocated its assembly operations from Bloomington, Indiana to Mexico. The buildings remained empty until purchased by Cook Pharmica in 2004.

Continued on page 10.

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

Congratulations Cook Pharmica
Winner of the Facility of the Year Award for Facility Integration



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for FACILITY INTEGRATION

We are proud to have supported Cook Pharmica with **leading-edge modular cleanroom facilities** for the development and manufacturing of mammalian cell culture-based biopharmaceuticals.



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"Modular cleanroom construction helped move the project forward with speed, even during inclement weather conditions, and significantly reduced waste and construction materials."

The factory consisted of two independent buildings each with approximately 450,000-sq-ft. Project Phoenix focused on the renovation of a portion of one of the buildings, which had an architectural element that lent itself well to the type of biopharmaceutical manufacturing that was envisioned for the site.

The structure is comparable to an over-sized bi-level with an overlap that is approximately 90 ft. The span from the lower-level floor to the roof of the upper level is roughly 35 ft. This attribute, in addition to others, enables Cook Pharmica to grow and expand with ease by having the ability to suspend bioreactors through the floor allowing enough clearance to accommodate large-scale bioreactors up to 16,000L.

The renovation and construction of 124,000 sq. ft. includes office areas, a manufacturing train, a shell for a second manufacturing train, development laboratories, quality control laboratories, warehouse, and process utilities designed to support up to two manufacturing trains. Construction was completed in 10 months.

With the footprint available for future expansion already in place and a second, independent building of 450,000 sq.ft., Cook Pharmica's facility is poised to expand with clients' project needs.

Designing for Segregation and Flexibility

The open structure of the building enabled Cook Pharmica to easily create controlled manufacturing rooms within it, as well as a flexible facility layout. The modular approach was used in the manufacturing areas.

Modular wall construction incorporated built-in covings for air returns and utilities and a walkable ceiling which would allow maintenance to be performed without shutting down the manufacturing areas.



Modular cleanrooms under construction.



Completed cleanroom area.



Mobile processing equipment.

Modular cleanroom construction helped move the project forward with speed, even during inclement weather conditions, and significantly reduced waste and construction materials. The modular approach also helped increase flexibility, allowing Cook the ability to move large pieces of equipment in and out of rooms or even modify the manufacturing facility layout itself. This enables Cook to grow and expand capabilities as the needs of their clients grow.

The design of the manufacturing train was segmented into four major areas based on the process step; cell culture, harvest, initial purification, and final purification.

Flexibility of the manufacturing systems allows for sound,

process-oriented production. There are very few pieces of fixed equipment throughout the production line, which allow for multiple configurations that can accommodate various processes.

The equipment in the cleanrooms consists of the latest processing systems. The centrifuge piping and TFF skids, for instance, incorporate the latest technological advantages to ensure cleanliness and maximum processing flexibility. Additionally, the process control

system can recognize mobile equipment regardless of location. These innovations provide opportunities for an economic scale-up that is client process-driven.

Keeping It Simple with Disposables

A component that is seen throughout the manufacturing area is the innovative use of disposables. The design team minimized the use of stainless steel equipment as much as possible in efforts to reduce the turn-around time and risk of cross-contamination between manufacturing runs. Disposable equipment can be found in every process area.

Continued on page 12.

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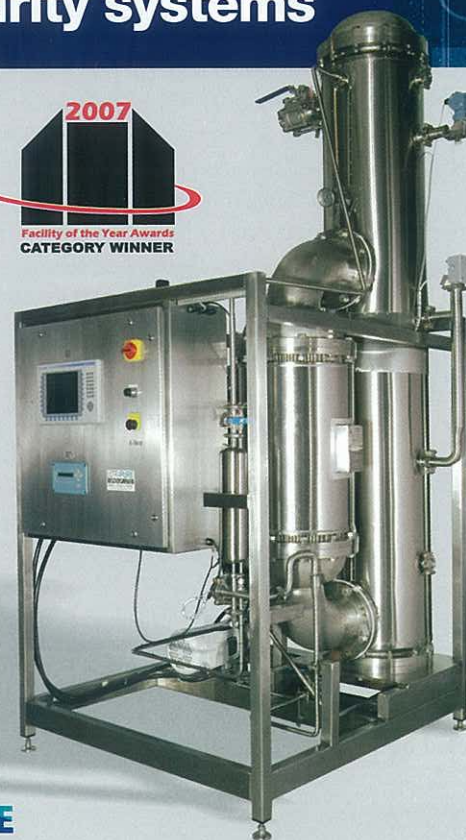
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Disposable bioreactor.

Bioreactors are utilized in inoculation prep as cells are scaled-up from shaker flasks to small-scale bioreactors (25L). Next, the cells are transferred to the cell culture room and into a larger bioreactor (100L) before moving into the stainless steel bioreactors.

Disposable bag technology was included in the manufacturing train and development laboratories. Disposable technology is also used for raw materials, media and buffer bags, intermediary product, filters, and bags with agitators.

Sterile bags significantly reduce cleaning validations and risk of contamination. Bag technology reduces production turn-around time, which translates to time and cost savings. Clients can choose how much disposable technology they want to use in their manufacturing project.

Another novel approach in the manufacturing area is the utilization of disposable bags for media and buffer transfer through wall pass-throughs. This design element allows media and buffer disposable bags (totes) to sit outside the manufacturing rooms and have the contents transferred through sterile disposable tubing to the appropriate equipment. This is another approach that helps reduce the risk of contamination during the manufacturing process.

The Benefits of Not "Over-Engineering"

There was a concerted effort to not "over-engineer" the project. Cook Pharmica spent less than 9% on total engineering costs, which is considered an exceptional accomplishment for a project of this type and size. Equipment was ordered "off the shelf" when possible to ensure timely delivery and to avoid unnecessary special equipment cost upgrades.

When constructing Phase I of Project Phoenix, more capital than needed was spent in order to keep a strategic focus on the ability to rapidly expand in the future. The utilities were oversized to be capable of bearing the load of the projected build out of Phase II.

By doing this, several things will be accomplished: 1) time will be saved by not having to commission and validate additional utilities, 2) money will be saved since it would have



Wall pass-throughs.

cost an estimated 40% more to add additional utility equipment for Phase II if Cook had not elected to over-size Phase I, and 3) Phase II is estimated to be delivered in 12 to 18 months as a result of this decision.

Promoting Transparency

The Cook Pharmica facility was designed to promote transparency in the manufacturing process.

Clients, inspectors, and visitors have access to a viewing corridor that runs parallel to the manufacturing

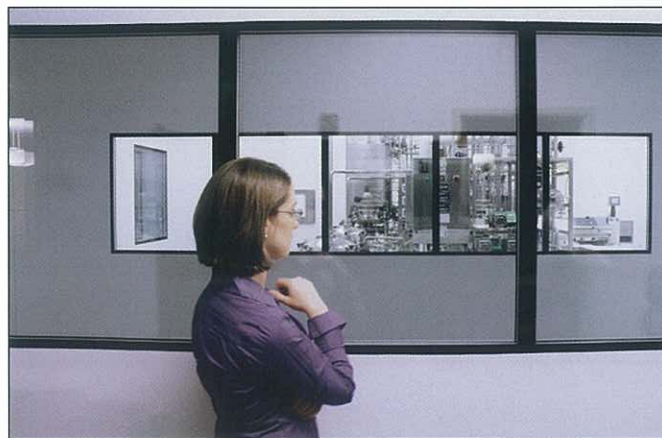
block. This feature was designed to provide full visibility at each stage of production, allowing visitors to monitor their projects without entering the manufacturing area. The laboratory areas also feature large windows for clients and visitors to view projects without actually entering the laboratory.

Real-time web cameras were installed to allow clients to view their projects from anywhere in the world. Cook Pharmica also extends this accessibility to regulatory agencies with client approval.

Energy Management Enhanced

Throughout the renovation, great effort was made to enhance energy conservation. A new roof was installed directly over the existing one and a façade was constructed along the exterior walls. These two improvements essentially provided a building with double insulation. The majority of the facility's floor expanse is built on grading allowing the ground's thermal heat to assist in maintaining the interior temperature of the building.

Throughout the interior of the building, elements were chosen to further enhance energy management. Every light fixture utilizes electronic ballasts, reducing the wattage usage by 50%. Each of the four walk-in coolers installed



Viewing corridor.

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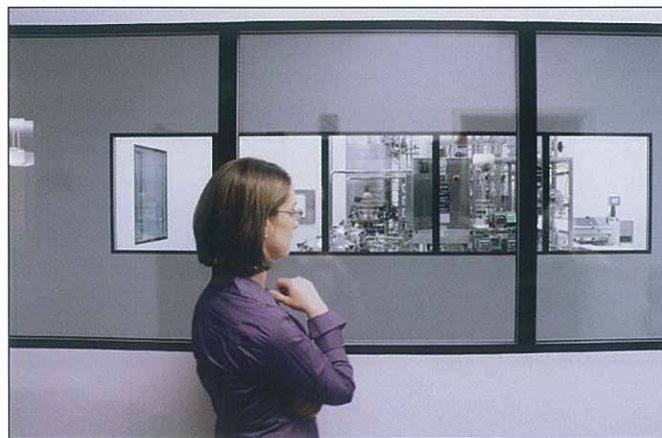
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Viewing corridor.

throughout the facility have an "R rating," the highest category for thermal installation.

In case of power failure, two diesel back-up generators were installed to prevent critical systems from losing power, to prevent impact on product quality. Cook Pharmica also performed a coordination study to ensure the facility was designed to be the most energy efficient.

Revitalizing a Community

The local economic environment improved as a result of Project Phoenix. Prior to construction, the surrounding neighborhood of McDoel lacked significant commerce activity and property values were stagnant and low. However, following the construction of Project Phoenix, four new businesses were established in close proximity to the facility and property values increased substantially in the area.


The area also is now a declared Life Sciences Cluster by the state of Indiana. Because of several new initiatives in Bloomington, along with the presence of Cook Pharmica and other companies in the life sciences industry, the local Ivy Tech Community College received a state grant for a Biotech Training Institute. This program offers degrees focused in the life sciences and will train future resources for companies serving the life sciences industry such as Cook Pharmica. Graduates of the program have already served as interns and in some cases been hired on as full-time employees.

Partnerships were established with local equipment and systems contractors whenever possible as well as national contractors. Contractors were tasked to install the best technology into the facility based on their expertise of design and the systems they built. Local contractors with limited industry experience were trained by Cook employees and consultants as part of the project. This approach led to increased dedication among vendors and contractors and consequently improved project quality and speed.

A further benefit of this approach is that the contractors are now prepared and trained for any future expansion opportunities. By taking the initiative to develop its future resources locally, Cook Pharmica is prepared to grow rapidly with client and industry needs.

The Standards of Quality

The quality unit took an active role in Project Phoenix from conceptual design through construction to ensure the facility was built suitable for intended use. Quality standards utilized throughout construction and commissioning and continuing into normal operation include:

- FDA regulations and guidances
- EC Guide to Good Manufacturing Practice, Annex 1
- EC GMPs for Active Pharmaceutical Ingredients, Annex 18
- ICH Guidelines
- GAMP®
- ISA-S88 and S95 standards
- ISPE Baseline® Guides, Vol. 4 Water and Steam Systems, Vol. 5 Commissioning and Qualification, and Vol. 6 Biopharmaceutical Manufacturing Facilities 

MUSSETT NICHOLAS + ASSOCIATES

MNA congratulates
~ Cook Pharmica ~
2007 Category Winner



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Genentech

NIMO's Journey

The word "journey," more so than "project," might better describe Genentech's Oceanside Product Operations in Oceanside, California, USA. During the six years it took to construct the six-building, 500,000 sq. ft. master planned 60-acre campus, the project involved three different owner companies and several facility modifications for various product requirements.

Genentech's Oceanside Product Operations project (also known as New IDEC Manufacturing Operations, or NIMO for short), is the winner of the 2007 Facility of the Year Award for Project Execution. Genentech is a leading biotechnology company that discovers, develops, manufactures, and commercializes biotherapeutics for significant unmet medical needs.

Upon US FDA licensure expected in the first half of 2007, the facility will add 90,000 liters of capacity that initially will be dedicated to producing Avastin® (bevacizumab), a cancer therapy and monoclonal antibody.

A united project team focused on the process as much as the end product successfully drove the facility through ownership and product complexities, making NIMO one of the most advanced facilities of its kind in the world. Not only does NIMO set new standards in biotech process design and automation, but also in project execution and delivery.

Changing Gears

A small San Diego biotech company, formerly called IDEC Pharmaceuticals, Corp., made the strategic decision in 2000 to build its first large-scale biotech manufacturing facility near its San Diego headquarters after it had successfully developed and commercialized its first product, Rituxan® (Rituximab) in cooperation with Genentech. Originally, the NIMO facility was designed for the IDEC pipeline.

Genentech

Category Winner – Project Execution

Project: Genentech Oceanside Product Operations (a.k.a. NIMO)

Location: Oceanside, California, USA

Architect: Ferguson Pape Baldwin Architects

Engineer: CRB Consulting Engineers, Inc.

Construction Manager: DPR Construction, Inc.

Size: 500,000 sq. ft. (46,452 sq. m.)

Cost: US \$375 million (base project)

Product: Avastin® (bevacizumab)

But, while the facility was under construction and more than half way complete, in November 2003, IDEC merged with Biogen, Inc. to form Biogen Idec, Inc. Soon after, it was decided that the multiple sclerosis treatment and monoclonal antibody Tysabri® (natalizumab) would be made at the facility. The facility was then modified to accommodate the manufacturing of that product.



Exterior view.

In June 2005, Genentech acquired the facility to increase its capacity for producing Avastin®. Again, the facility was modified to manufacture that product.

Despite ownership changes and facility modifications, the team stuck together and successfully responded to the business needs of each owner company, while delivering the base project on time and under budget.

The team largely credits their success to their unique "Design-Build Hybrid" approach.

The "Design-Build Hybrid" Team and Approach

A team consisting of the owner, engineering company, architect, and general contractor was formed and developed an innovative project delivery approach that is best described as a "Design-Build Hybrid." In this approach, civil, architectural, and structural work were executed design-bid-build, and mechanical, electrical, process, and instrumentation and controls (I&C) were completed design-build under leadership of the general contractor.

In order to achieve consistency in

Continued on page 16.

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CRB Congratulates Genentech

Winner of the Facility of the Year Award for Project Execution Oceanside Product Operations (NIMO)



Congratulations Genentech and thank you for allowing CRB to be part of an exceptional team and incredible experience. The dedication to teamwork truly brought down the individual corporate agenda walls and enabled a talented team to focus on the success of the project. The team certainly "Enjoyed the Journey".

— Sean Eickhoff, CRB Consulting Engineers



FPBA was thrilled to be a part of this team. The collaboration between everyone involved was key to the project's success. CRB was an incredible team player with great technical experience.

— Jim Ferguson, FPBA Architects



Rarely, if ever, has a facility of this scale, magnitude and significance been delivered in such a collaborative manner. The commitment to building a team that can be trusted and empowered resulted in an extraordinary outcome and an unparalleled experience for each of the partners on this project.

— Jay Leopold, DPR Construction



CONSULTING ENGINEERS, INC. ■

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Buffer prep modules.



Valve array.

project standards and quality, the owner, architect, and general contractor all unanimously selected an engineering company to oversee all engineering performed by the design-build contractors in the mechanical, electrical, process, and I&C engineering disciplines.

To further ensure success of this innovative delivery approach, during the engineering and early construction period, the team moved under one roof in office space eight miles from the construction site. With the office as the center point of all design work, the project team avoided the typically extensive project travel while increasing cross-functional communication and enhancing the focus on budget and schedule.

Largely due to the Design-Build-Hybrid approach and people-oriented execution focus, the team delivered – on time and under budget – a facility that features unique innovations, design advancements, and quality attributes, including large-scale modular construction (super skids), an advanced degree of automation systems, a high level of system integration, flexibility and adaptability within the manufacturing building, and expandability of each functional area.

Process Design Flexibility

The NIMO facility possesses all typical unit operations and equipment used in large-scale mammalian cell culture manufacturing technology. However, the team ensured that the facility design was able to accommodate a relatively wide range of monoclonal antibody processes. Due to the high degree of built-in process design flexibility, the process design and automation was modified for each product/company change for less than 5% of the initial capital investment and minimal downtime. Some highlights of this flexibility include:

- There are dedicated cleaning equipment and CIP processes for each functional area of the operation. Virtually the entire process operation is cleaned by fully automated CIP systems.
- The number, size, and connectivity of the buffer preparation vessels and buffer hold vessels confer considerable

flexibility on the facility.

- Valve arrays are strategically designed and used to permit transfer of product from one unit process to another and for supporting operations such as media and buffer transfers. Many of these operations also may occur in parallel. By modifying some of the valve arrays, the order of the purification steps was changed without major impact to the process design.
- The harvest area of the facility was designed to allow both a centrifuge and multi-step filtration to clarify the cell culture fluid after the fermentation step. With minor re-configuration, the harvest step was modified to accommodate a different monoclonal antibody process for IDEC, Biogen Idec, and Genentech.

Reaching New Heights in Automation

Automation and system integration were taken to new industry levels at the NIMO facility. From the start, it was the team's vision to build a fully automated facility and minimize

ISPE Guides NIMO Commissioning/Validation

The NIMO commissioning and validation team used the *ISPE Commissioning and Qualification Baseline® Guide*, published in 2001. The team followed all steps of this guide for system and equipment validation. In addition, the *ISPE GAMP® Good Practice Guide for Calibration Management* was used. Systems' assessments (direct, indirect, and no impact) and component criticality assessments were rigorously executed and systems boundaries were defined. For the Manufacturing Controls System and the Building Management System, the validation team followed the *ISPE GAMP® Guide for Validation of Automated Systems*.

the manual operating steps. The primary objectives of the automation were to reduce cycle time, increase operational efficiency, reduce manual work and operator errors, improve product quality and consistency, and enhance safety while providing controlled and immediate access to process data.

The Manufacturing Control System (MCS) provides coordination of the manufacturing operations by managing the required resources and execution of operations. Complete batch histories of operations performed are maintained by the MCS for reporting and archival.

Manufacturing operations controlled by the MCS system include media prep, fermentation and harvest, buffer prep and hold, and purification and formulation. In addition, the following utilities and support operations are controlled by the MCS system: CIP, SIP, AWF/HWFI distribution and usage management, and clean steam distribution.

The MCS operations include bar-coding of all materials under the control of the MCS and within the manufacturing envelope, automated and complete lot genealogy, including full forward and backward material and container traceability and all material codes. Operational status information on materials under control of the MCS (e.g., material in a fermenter) is also available from the MCS. Usage and expiration management are tracked by the MCS for media solutions, buffers, resins, supplies and components (filters, tubing, hoses, bags, etc.) AWF/HWFI, CIP (clean, dirty hold times), and SIP (expiration applicable only while pressurization is maintained).

Process management, unit supervision, and process control provide automation of process and equipment activities at the process cell unit (unit operation) and equipment module level. Work orders (recipes) scheduled by a campaign management application are implemented by the process management control activity. Production information management provides for collection, processing, and reporting of process data.

A campaign management application was chosen for the Manufacturing Execution System and was coupled with the MCS. The application resides in the control system plant server and serves as an interface for handheld Portable Data Terminals (PDTs). The PDTs are used to scan in raw materials that are used in the process, verifying the materials are not expired and are being used in the proper location by requiring the PDT in operation.



PDT in operation.

Concludes on page 18.



Electrol Specialties Company



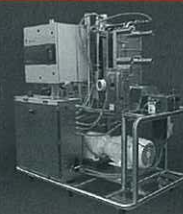
CIP Process Design

Congratulations

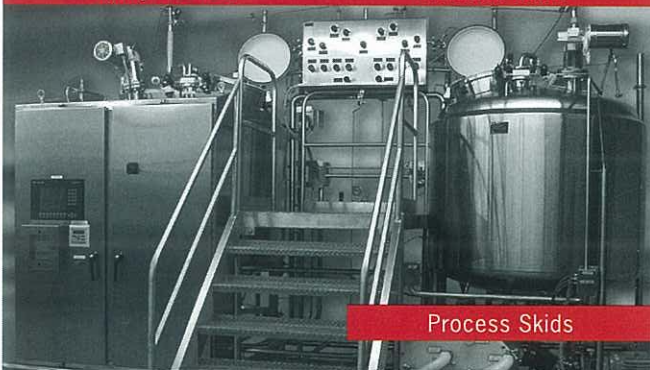
Electrol Specialties Company (ESC) salutes our Genentech Oceanside and Cook Pharmica clients for being named as finalists for the ISPE Facility of the Year awards. We are proud to have been named as a primary project partner by both facilities for providing CIP process design, equipment, spray devices, and field support.



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The spine.

operator to scan the point of use. The integration of a campaign management application united with an historical data collection product provides a full product genealogy from cell thaw through final bulk production.

Super Skids and a Spine

According to Genentech, the project is one of the first biotech manufacturing facilities to successfully use the concept of large modular equipment design (i.e., super skids). Super skids were used in buffer prep, buffer hold, media prep, fermentation, harvest, purification, and formulation.

Overall, more than 70 process tanks and 18 fermenters were integrated into 17 modules or super skids. This approach offered three key advantages: overall construction time savings, reduced on-site construction labor, and highest construction quality.

The design team placed much effort on combining functionality with architectural beauty. All six buildings are connected by a "spine" that not only efficiently distributes plant and clean utilities, but also provides for enhanced material and product flows from and to each building. This "spine" can be extended to allow for the expansion of each function on site. Each building, including the "spine," and even the core of the manufacturing building, also permits an abundance of natural light.

Commitment to Quality

In order to deliver a coordinated facility design, the project was broken down into its six buildings with each building considered one project managed by a Building Area Team (BAT). Each BAT coordinated its design requirements on a weekly basis with individual mechanical, electrical, plumbing, process, and automation discipline teams to ensure design consistency across all BATs.

The BATs adopted a commitment to a "Zero Defects" goal by which to measure project quality success. To meet this challenge, the NIMO team organized quality inspection teams made up of BAT members, trade contractor representatives, third-party inspectors, and City inspectors.

These inspection teams successfully maintained a Zero Defects approach during construction by employing a quality plan that included construction of mock-ups to review and define quality requirements; approval and recording of "first-

in kind" benchmarks to address the quality of repeating design elements; in-wall and above-ceiling preclosure inspections to ensure coordination with design installation requirements; field operational testing inspections to ensure that systems met functional requirements, a field observation reporting program to identify discipline specific consistency items; an equipment receiving inspection program to document the state of the equipment arriving at the site; and a commissioning acceptance program to execute the start-up and commissioning of building systems and equipment in support of the installation qualification phase.

The team's commitment and disciplined mindset to quality during construction laid the foundation for the high state of GMP compliance in commissioning, validation, and early GMP operations.

Collaborating for Increased Environmental Protection

The NIMO facility is located on Eocene-age (36- to 57 million-yr-old) and Pleistocene-age (11,000 to one million-yr-old) deposits, known to be of fossil bearing potential.

The NIMO team worked with local governing agencies and the San Diego Natural History Museum to implement a mitigation plan whereby contract paleontologists and Museum staff paleontologists would work in concert with the grading contractor to identify fossil deposits in the field for collection and removal.


During mass grading, this group discovered the skull fossil of a 40 million-yr-old Brontothere – an ancient cousin to the modern day rhinoceros. These remains are now on display at the San Diego Natural History Museum.

In addition, the owner received an Environmental Responsibility Award from the City of Oceanside for its collaborative efforts to prevent storm water pollution, as well as worked closely with the City to negotiate a brine wastewater outfall expansion that relieves the city of special treating up to 155,000 gallons of wastewater per day.

Energy Efficiency

Although manufacturing facilities do not typically allow for energy saving opportunities, every effort was made to increase energy efficiency through the use of a low voltage lighting control system, variable frequency drives, variable air volume system, and building management system controls. In fact, San Diego Gas and Electric awarded a one-time rebate of \$176,785 due to these lower energy usage controls.

Operational Excellence

NIMO has shown excellence in early operations. The first test fermentation batch of Avastin® attempted was successfully completed and made Genentech history in September 2005 with the largest amount of therapeutic protein ever made in a mammalian cell culture fermenter. Following the completion of all Avastin modifications in February 2006, seven Avastin qualification lots were completed in seven consecutive runs and passed all additional comparability tests when compared to Avastin manufactured at other Genentech sites. 

Congratulations Genentech
Winner of the Facility of the Year Award for Project Execution

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Shanghai Roche Pharmaceuticals Limited

Project Execution Success in China

In just two short years and with a modest budget, Shanghai Roche Pharmaceuticals Limited constructed what may be the first high containment facility in China. The Shanghai High Potent Production Project (SHiP), located in Zhang Jiang High Tech Park in Shanghai, China, is the winner of the 2007 Facility of the Year Award for Project Execution Regional Excellence.

Shanghai Roche is a joint venture with Sunve Pharmaceuticals of Shanghai, China which has been operating successfully for over 10 years. The new SHiP facility was added into the existing site so as to extend its scope to manufacture highly active tablets and capsules for the China market and for export into the Asia Pacific region. These highly successful products are for the prevention of organ rejection in transplant recipients and for the treatment of specific forms of cancer.

China is administratively complex and requires innovative approaches to work with the cultural, historical, and language challenges. Yet from conception to reality, the SHiP exceeded project goals through speed, innovation, and global teamwork. The result: a facility that uses global and local resources to manufacture key strategic products for the local market and export. According to FOYA Judges, this is what distinguishes SHiP as an award-winning project.

The Business of Boosting China

Shanghai Roche's business plan foresaw a large increase in the sales of two of its main products in China. Xeloda® is a product for various types of cancer, and Cellcept® is an effective immunosuppressant for organ-transplant rejection in patients receiving allogenic renal, cardiac or hepatic transplants. The challenge for the local business team was to double sales in less than four years, which provided an

Shanghai Roche Pharmaceuticals Limited

Category Winner – Project Execution Regional Excellence

Project: Shanghai High Potent Production Project (SHiP)

Location: Shanghai, China

Architect: Meissner & Wurst Zander (Shanghai) Limited

Construction Manager: Meissner & Wurst Zander (Shanghai) Limited

Project Manager: Shanghai Roche Pharmaceuticals Limited

Size: 22,604 sq. ft. (2,100 sq. m.)

Cost: US \$16.64 million (CHF 22.47 million, September 2004)

Products: Cellcept and Xeloda



Exterior view.

exciting and challenging background for the project.

In late 2003, it was decided that local manufacturing of these highly active products could provide a real boost to growth in the China market. The business case for the SHiP facility was based on a targeted investment in local manufacturing to support the growth of the market for these highly active products rather than a classic cost reduction strategy.

This investment presented the company not only with the opportunity to grow the local market, but to help develop the local skill base and become a regional supplier for Roche. As the supply of pharmaceuticals becomes more and more global, this allows the site to grow into a more important role for the company.

The Difference Diversity Makes

The entire project comprised construction of a new building in the middle of an existing site for the production of highly active medicines with strict containment. The scope of the work included all planning and design stages and construction, including the piled foundations, reinforced concrete superstructure, all building finishes, and the complete installation of all necessary services, including sourcing, installation, commissioning and qualification of the required plant and equipment.

Staff and equipment came from a large number of different countries and

“Since the budget for this project was not large, technology was used in clever ways to achieve a contained process.”

cultures. The main equipment was imported from Switzerland, Germany, England, and Italy. The team comprised staff from Switzerland, England, Germany, France, Italy, Turkey, South Africa, Australia, and China.

Because equipment was sourced from many different vendors, integration was an important aspect for the project. New equipment had to be retrofitted to work in conjunction with existing equipment. Local products were used as much as possible to ensure that all main equipment could be correctly and fully utilized.

The validation teams planned and executed all validation activities in parallel to ensure the facility was productive in the shortest possible time. At the same time, it was necessary to keep all of the existing site functions fully operational without interruption.

SHiP's Containment Philosophy

Within the Roche group, this project is the first self-contained and dedicated production facility for the manufacture of highly active medicines and to the company's knowledge, the first high containment facility in China capable of meeting international standards of quality.

Since the budget for this project was not large, technology was used in clever ways to achieve a contained process. The design ensured the minimum number of workers were required (who could be potentially exposed to the product), and enabled the application of technology in ways to allow for efficient processes.

Key to the success of the containment philosophy was the isolation valve system which would be used. Data from valve system testing results were reviewed from all of the potential

vendors prior to making the final choice. This included measurements of the particle containment of the system and testing of the various blowing and exhaust vacuum cycles needed to clean the valve surfaces prior to equipment separation. The valve system chosen was able to meet project requirements both in terms of containment ($<10 \mu\text{g}/\text{m}^3$ room air) and budget.

After the valve system to be used was decided, one of the key issues to address was how to integrate that system into equipment from different sources. A decision was made to order the bins, lifting columns, and bin washing station from the same vendor to minimize integration issues. Extensive work was needed with vendors of other equipment on how to integrate the valves and their control system in an efficient way.

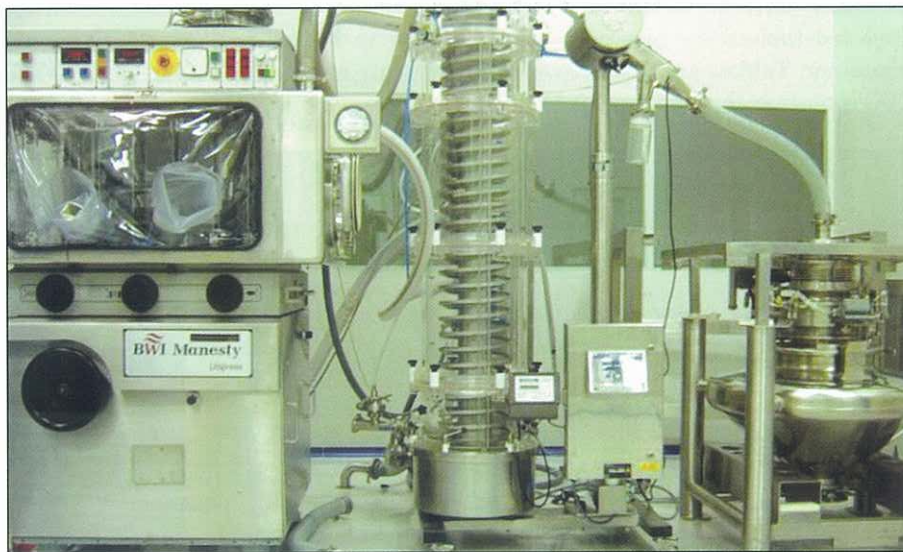
In some cases, local expertise was used to integrate existing equipment, which was transferred to the new facility when investment in new equipment could not be justified within the budget. This presented the project team with the challenge of how to use equipment not designed for high containment in a facility where the target dust levels are $<10 \mu\text{g}/\text{m}^3$ room air. Innovative solutions had to be found that could reach the high quality and safety standards, while fitting in a comparably low budget.

For example, an innovative design was used to retrofit isolator technology to the tableting machine, ventilate the working cabinet to ensure containment, and change the feeding chute to incorporate an isolation valve. The team successfully changed the machine to meet the criteria for routine operations.

Wet deduster systems were chosen for the facility and are connected to the main pieces of equipment. Separate dedusters service the major equipment. They have been designed to allow water back flush in such a way that the risk of cross contamination has been eliminated. This ensures that API dust from the process is collected safely and fed to a waste neutralization plant without risk to the staff or environment.



IBC container ready to be joined to the isolation valve.



Tablet press retrofitted with isolator and new ancillary equipment added.

Continued on page 22.



Wet dedusting systems.

Designing Equipment for the Highly Active

Much of the equipment is traditional but required additional thought and design consideration to enable an acceptable high potent function, especially in cleaning systems.

For example, the existing tablet press was retrofitted with an isolation valve and an isolator. The isolator allows routine operation of the press to meet containment requirements. The new enclosure has glove ports on three sides with innovative safety systems which shut down the machine should an operator attempt to use the gloves while the machine is operating.

A pass box allows dust-free transfer of cleaning materials into the tablet press. After initial wipe down to reduce dust as much as possible, the flexible enclosure windows of the isolator can be removed and the machine fully cleaned.

The granule container is lifted by means of a post hoist onto the isolation valve mounted directly on top of the tablet press feed pipe. The valve allows dust-free transfer of granule directly into the tablet press.

Upon compression the tablets pass through a high potent compliant deduster with integrated metal detector. Sample tablets are discharged into a small container with a small isolation valve to minimize dust reaching the room air. Rejected tablets are also collected separately in a sealed container. Tablets are then passed by gravity into a waiting IBC container through an isolation valve.



Inhibace granulation.

Keeping Pace with China's Market

Because China is a fast-growing market, it was difficult to establish a reliable forecast of the required capacities. A decision was made early in the project to allow for production room sizes which could incorporate larger equipment than that required for the initial forecasts. This way, increased volumes could be proven before the need to invest in larger equipment, and cost savings could be made adapting some existing equipment.

This strategy proved effective, as the requirement for capsules outgrew the capacity of the original machine intended for the encapsulation area. Midway through the commissioning phase, the transfer of the existing encapsulation machine, which has a capacity of 18,000 capsules per hour, was deleted from the project.

A new credit was arranged and an encapsulation machine with a capacity of 100,000 capsules per hour was ordered to replace the existing machine. The machine has the capacity to be upgraded to 150,000 capsules per hour.

Built-In Safety

Safety awareness – still evolving amongst the local workforce in China – was a key aspect for the project during all construction phases. Staff were issued a site security pass only after undergoing appropriate safety training. With more than 275,000 man hours worked during the total construction, there were no working days lost due to accidents during the project.

Worker safety is enhanced inside the facility in several ways. The airlock system for each room is designed to allow the segregation of the flow of personnel from materials and equipment. The personnel side of the airlock provides a segregated area for decontamination with easy to use emergency showers in the event of an accidental release of product dust. Door interlocks and room pressure cascades ensure that there is an extremely low likelihood of product particles reaching the central corridor.

Environmental Awareness

Environmental awareness is another area which is becoming increasingly important in China. This presented the following opportunities.



Dispensing isolator.

"...the SHiP's crew used global and local resources to build a cGMP facility that now manufactures key strategic products for the local market and export."

The project was able to draw on the resources of the Roche Head Office in Switzerland to develop plans for ensuring adequate environmental protection.

To meet a corporate directive regarding ozone depletion, ammonia chillers were installed for the project. These are rare in China and local companies do not have much experience with them. This decision was met with some early local resistance and presented some problems during equipment start-up due to this lack of local experience.

Waste water was of primary concern for the project because any residual active product on the equipment ends up in the waste stream during the cleaning process. The solution was to create a special tank to collect waste water generated during the cleaning of equipment. All drains from the production workshops lead to this tank, which is separate from sanitary waste.

The waste water is treated in a specially designed treatment plant which ensures that API levels are significantly reduced to acceptable levels before discharged into the normal biological waste treatment plant for the site.


Due to the nature of the APIs in use in the building, the HVAC system was designed to use 100 percent fresh air. In order to minimize energy requirements, the HVAC systems were fitted with heat recovery systems to return heat from the exhaust air to the incoming air. Extract air handling systems are provided with H13 filtration to ensure API does not reach the outside air.

Dust extraction systems use water filters to collect dust residue and this water drains to the special collection tank for plant waste water previously described. Dry police filters are fitted to these machines in case of failure of the water filters.

The Proof is in the Production

Application of good engineering practice and quality management was used to improve efficiency in time schedule, cost, and quality for the project. As a result, the project was able to gain GMP approval from the local regulatory authorities, achieve budget and schedule targets, while providing a safe and environmentally responsible work place for 650 employees.

The project has demonstrated that with a modest investment, it is practical to build a compliant factory which can drive business growth. Innovative approaches were applied to optimize the use of new and existing equipment.

Instead of executing the whole project with an overseas team and imported equipment, the SHiP's crew used global and local resources to build a cGMP facility that now manufactures key strategic products for the local market and export. The rapid growth in production of Cellcept and Xeloda exemplify this success. 

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Taiyo Pharmaceutical Industry Co., Ltd.

Pre-Filled to Perfection in Japan

In response to the demand from Japan's medical community for pre-filled syringes with the utmost quality and functionality, Taiyo Pharmaceutical Industry Co., Ltd. embarked on a project that would not only meet market expectations, but advance the industry's aseptic processing technology.

Taiyo's Unit Factory Building Pre-Filled Syringe (PFS) Manufacturing Facility is the winner of the 2007 Facility of the Year Award (FOYA) for Equipment Innovation. The six-story, 11,744 sq. m. PFS Manufacturing Facility is located at Taiyo's Takayama Factory site in Takayama City, Gifu, Japan.

The project currently produces a total of six products, including four plastic syringe containers and two glass syringe containers. In addition to manufacturing its own syringe containers in-house, two other manufacturing lines, equipped with high-speed type isolators, have been successfully completed and produce pre-filled syringes.

Taiyo's manufacturing equipment and processes for production of outstanding quality syringe containers and a unique silicone inspection system are some of the innovations that impressed members of the 2007 Facility of the Year Awards Judging Panel.

Trial by Error

Taiyo's main business comprises two major enterprises: contract manufacturing and the production of generic products.

The company had once relied on purchasing syringe containers from external suppliers for its pre-filled syringe preparations. But Taiyo discovered that the level of function-



Exterior view.

ality and quality of purchased containers varied or were not meeting the company's and medical community's increasingly high requirements for pre-filled syringes.

Major problems associated with PFS use by the medical community included poor sliding action, poor seals, Luer damage, and shape deformities (pinhole blockages, etc.).

Taiyo had no way of checking the mechanisms or functionality within its own manufacturing process and no way of preventing the on-flow of poor quality goods. For example, Luer pinhole damage was not detectable until the product was actually in use at a medical institution.

Quality issues caused repeated inconvenience to medical institutions and Taiyo's clients. In addition, the cost of purchasing PFS containers accounted for a large portion of the overall manufacturing cost.

In response to the needs and requirements of the medical community, and the company's own business strategy to provide low-cost, high quality pre-filled syringes, Taiyo began full-scale production of PFS containers in 1996. Currently, Taiyo's plan is to produce and deliver a reliable supply of approximately 50 million plastic and glass pre-filled syringes to the market.

In addition, Taiyo has joined forces with external container manufacturers to develop a variety of design improvements to PFS containers.

Taiyo Pharmaceutical Industry Co., Ltd.

Category Winner – Equipment Innovation

Project: Unit Factory Building Pre-Filled Syringe (PFS) Manufacturing Facility

Location: Takayama City, Gifu, Japan

Designer (Production Facilities): Horiuchi Architectural Associates

Designer (Production Equipment): Taiyo Pharmaceutical Industry Co., Ltd.

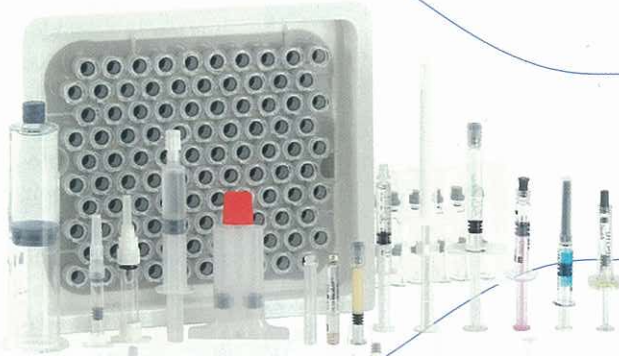
Construction Management: Kashima Construction K.K.

Size: 126,411 sq. ft. (11,744 sq. m.)

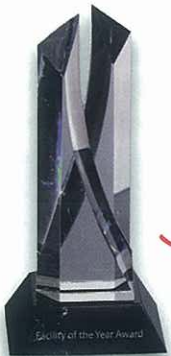
Cost: US \$38.58 million (JPY 4,580,000,000)

Products: plastic and glass syringe containers, pre-filled syringes

Special machines for the pharmaceutical industry!

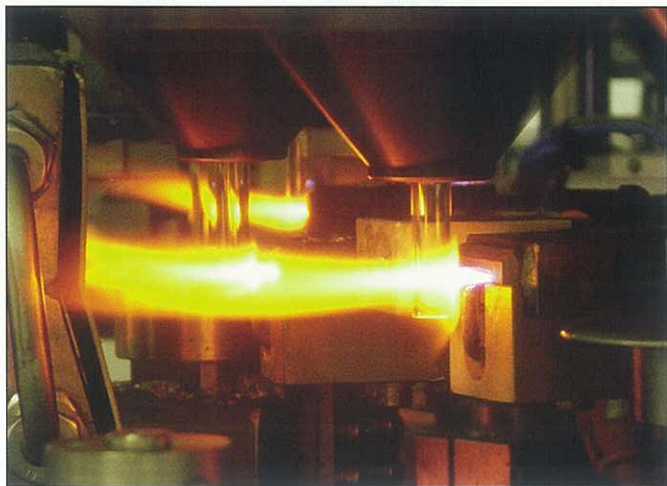


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Luer part molding process.

The Merits of Manufacturing In-House

The merits of moving ahead with the project of manufacturing PFS containers in-house, according to Taiyo, are as follows:

- reduction in purchase cost of PFS containers
- ability to make improvements to the basic functionality and quality of the processed goods, while incorporating new functionality requests into the PFS design
- design the PFS container production line to ensure high quality of products, while maintaining a stable production line

Taiyo's target is to reduce the costs of both plastic and glass syringes by approximately one-fifth to one-half compared to the cost of purchasing supplies from container manufacturers. Therefore, with annual volume increases, proportional



Glass syringe barrel molding machine.

sterilization processing system, compared to the company's current production costs, they estimate they can achieve a one-third to one-fifth cost reduction in packaging.

Overview of Glass Syringe Manufacturing

The molded and annealed in-house manufactured glass syringe barrels are transferred under a Class 100,000 controlled environment via transfer trays and then automatically positioned, aligned, and stacked in multiple layers into a collapsible container where required quantities are loaded onto a pallet. Every pallet, as a unit, is stored automatically under a Class 100,000 environment, and then following the production plan, the required number of units are conveyed to the filling station in the facility's 4th floor.

Using these transfer trays under a Class 100,000 environment, the barrels on each transfer tray are serially controlled as a unit even during the transfer period, completely preventing direct human touch to the containers.

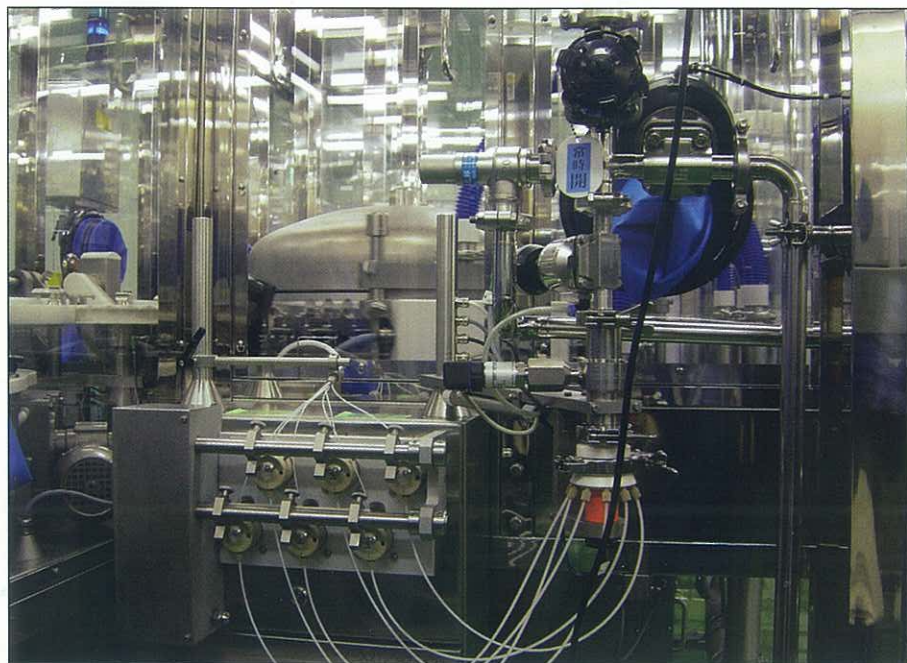
Unique Silicone Inspection System Reduces Sliding Defects

Although there are differences between glass or plastic type syringes and between emulsion or oil types, it is necessary that a given quantity of silicone be applied in a stable spray pattern, maintaining stable mist/particle sizes and minimal coating.

At Taiyo, the weight of coated silicone (silicone oil) is controlled to $2.5 \text{ mg} \pm 1 \text{ mg/pc}$ for a 5 ml syringe, currently the smallest volume among their in-house manufactured plastic syringes.

In the case of glass syringes, for a 1 ml-long syringe it is $5 \text{ mg} \pm 2 \text{ mg}$ where coating precision is a bit lower, being an emulsion type.

According to Taiyo, the company tries to improve its hardware (i.e., atomizing air, spray nozzle, quantitative coating



Silicone pump.

"...Taiyo instituted a new special real-time/in-line sensor to measure coated silicone amounts of all products, and if coating is out of specification, those products are expelled from the line."

pump, etc.) in addition to attempting to limit or suppress the coating amount variations caused by sporadic air seepage. Based on this knowledge, Taiyo said it is physically impossible to suppress the occurrence of sporadic air seepage to "zero," an issue which is aggravated by the inherent bubbles present in silicone fluid.

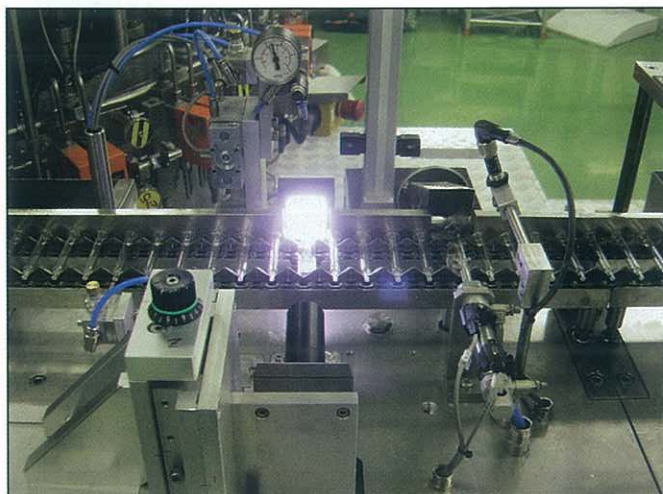
For these reasons, Taiyo instituted a new special real-time/in-line sensor to measure coated silicone amounts of all products, and if coating is out of specification, those products are expelled from the line.

The silicone coating inspection system is incorporated in the high-speed filling and packaging line for the manufacture of new 1 ml and 2 ml glass syringes. In this inspection system, if the coating is less than 3 mg (i.e., the low limit of 5 mg \pm 2 mg), all of the corresponding products are expelled as "no good," without fail, from the system.

By deploying this newly developed inspection system, defective products with "no silicone" or "deficient silicone" are not only prevented from progressing to the drug loading step, but also variations of sliding properties are reduced, enabling secure, stable, and reproducible sliding properties.

Original Inspection System for External Appearance, Dimensions, and Functionality

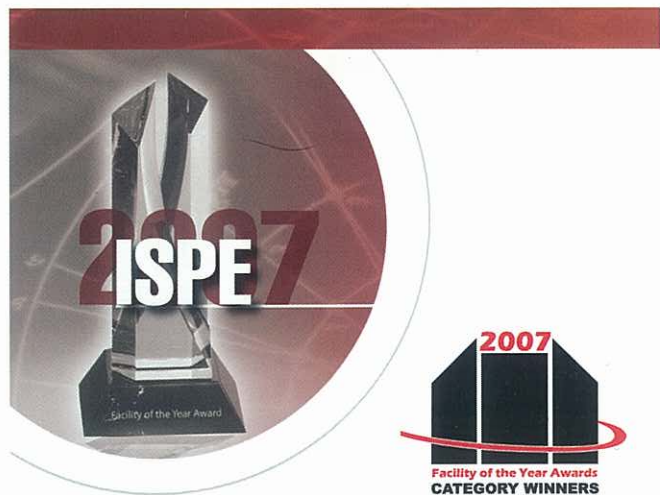
From the syringe barrel molding process to the filling and packaging processes, Taiyo is equipped with double and triple checking systems. As for defects that originate during Taiyo's own processes, according to the company, those defects are all discovered 100% by various detection systems



Luer internal diameter inspection.

Concludes on page 28.

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Facility of the Year
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**Genentech, Facility of
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*Oceanside Product Operations
(NMO) Project*



**Shanghai Roche
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Execution Regional
Excellence
Shanghai High Potent



**Taiyo Pharmaceutical
Industry Co., Ltd., Facility
of the Year Award Winner
in Equipment Innovation**
*Unit Factory Building PFS
Manufacturing Facility*



**Vetter Pharma-Fertigung
GmbH & Co. KG, Facility
of the Year Award Winner
in Process Innovation**
*New Facility Ravensburg Vetter
South (RVS)*

For more information about the Annual Facility of the Year Awards competition, please visit

www.facilityoftheyear.org



“From the syringe barrel molding process to the filling and packaging processes, Taiyo is equipped with double and triple checking systems.”

instituted in those processing steps and the defective parts are expelled from the system.

Furthermore, in order to guarantee processing qualities at an elevated level, Taiyo incorporated conditions of a steady state operation for manufacturing facilities as determined by the newly adopted Supervisory Control and Data Acquisition (SCADA) system.

In addition, in order to determine whether all defective products have been expelled from the system, Taiyo instituted a trend data system, making a production system capable of preventing 100% of defective products from advancing to the next processing step.

Fully Automated Loading and Unloading

To allow for sustainable, stable operations in each manufacturing step, it is necessary for PFS containers to be easy to handle, produce, sterilize, and inspect for shape, dimensions, and precision/tolerance. These needs are met with a fully automated operation for loading and unloading barrel transfer trays.



Overall view of tray loader and unloader.




Syringe barrel transfer tray feeding station.

At Taiyo, syringe barrels are molded at more than 300 C° under a Class 100,000 environment, and after the pyrogen-free molding stage, external appearance, dimensional, strength, and functional inspections are made for all the products within the processing steps.

Only the products that pass the strict inspections are allowed to move to transfer trays by a predetermined quantity, and then automatically integrated with the dedicated collapsible containers in a predetermined quantity of rows and layers.

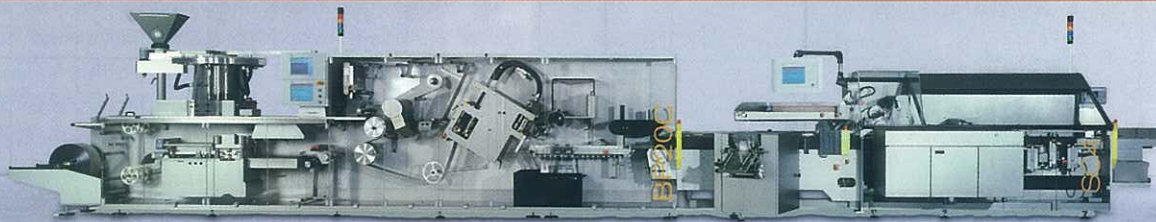
Thereafter, sustaining continued serial control, they are moved by an automatic transport carrier to storage in a Class 100,000 automated storage station, lot by lot storing and controlling. Only syringe barrels passed by the quality assurance department are automatically removed and arranged to the filling zone by an automatic transport carrier.

When it is necessary to split drug loading and packaging steps from vaccine and cold storage drugs, Taiyo's tray loading and unloading system is deployed to automatically transfer filled syringe containers to transfer trays, align and integrate them in a collapsible container, and then store them in a cold storage or Class 100,000 automated storage station.

The loaded syringes are automatically fed into downstream packaging steps in a similar manner by a tray loader and unloader system to finger grip and plunger rod attachment, labeling, and cartoning, while minimizing operator involvement. 

◦ FORWARD THINKING PHARMACEUTICAL EXPERTISE.

The pharmaceutical industry is faced with new challenges. Markets are becoming ever more dynamic, product recipes ever more complex, and innovation cycles ever shorter. Today IWKA PACKAGING meets these challenges with leading pharmaceutical expertise, which optimises all processes within the pharmaceutical production chain, and at the same time generates added value in every respect. From the powder recipe in the laboratory to the packaging on the shelf, from perfect planning to increased market availability.

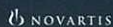


BP 20/SC 4 Blisterline

We congratulate TAIYO, winner of the
"Facility of the Year Award 2007"
for Equipment Innovation.



Our customers include:



The 2007 Facility of the Year Awards

Continued from page 6.

Submission Criteria

Award winning projects are those that are representative of a safe and productive manufacturing environment where the facility applies new or innovative technological solutions to meet a business need. Each project was evaluated against the following criteria:

- Essential Requirements (Must be included in all submissions)
 - Personnel Safety
 - Hazard Control
 - Environmental Impact
 - Energy Management
 - Access for People with Disabilities (if applicable)
- Significant Contributions to the Pharmaceutical Manufacturing Industry such as:
 - Applications of new technology or new applications of old technology
 - Advances in manufacturing technology
 - Advances in facility design technology
 - Advances in equipment design technology
 - Advances in commissioning/validation technology
- Project Uniqueness and Innovation
 - Originality
 - Systems Integration
 - Innovative Approaches/Developments
 - Systems/Facility Innovations
 - Flexibility/Adaptability
 - Facility/Process Integration/Process Innovation
- Quality
 - Quality standards
 - Response to Environmental Challenges
 - Response to Safety Challenges
 - Innovative Approaches to cGMPs
- Operational Excellence
- Excellence in Execution
 - Project Management
 - Budget Control
 - Organization
 - Innovative Project

Pharmaceutical Engineering Focuses on Winners

In addition to this issue, *Pharmaceutical Engineering* (PE) magazine will release another Special Edition to be distributed at ISPE's 2007 Annual Meeting in November. This upcoming edition, which will be mailed with your copy of PE's November/December issue, will take you behind the construction and competition curtains.

Articles will focus on the making of each facility, featuring exclusive interviews with the overall Facility of the Year Awards Winner and Category Winners. The issue also will include a candid interview with Andy Skibo, Chair of the FOYA Judging Panel, who will provide valuable insight into why the winners were chosen and the importance of this prestigious competition to the global pharmaceutical manufacturing industry.

- Delivery
- Response to a Business Plan
- Change Control
- Resource Management
- Schedule Control/Expediting

Criteria were not ranked or weighted. Projects that won these awards reflected the art of applied engineering and demonstrated the use of new technology, advanced applications of existing technology, or provided elegant solutions to routine issues. The projects were not necessarily massive or costly, but more importantly, represented the highest quality of design and engineering.

2007 Facility of the Year Judging Process

Submissions for the Facility of the Year Awards were reviewed by a volunteer panel of nine prominent industry experts with significant experience in various disciplines, including pharmaceutical engineering, construction management, and manufacturing. Submissions were reviewed individually by each judge prior to group discussion during a meeting of the entire judging panel. During the meeting, judges discussed the technical merits of each submission and were tasked with selecting the Category Winners, including the overall winner of the award.

Although past judges agree that the biggest challenge is to choose from such a diverse field of uniformly great facili-

ties, judges adhere to the detailed submission criteria in order to distinguish those facilities that are truly outstanding and worthy of being selected as a Category Winner or overall Facility of the Year Award Winner.

Meet the 2007 Facility of the Year Awards Judging Panel

Andy Skibo, Judging Panel Chair

Vice President Corp. Engineering and Capital Production, Amgen

Nigel Barnes, Vice President, Global Project Management, GlaxoSmithKline

Chaz Calitri, Senior Director/Team Leader, Pfizer Global Engineering


Christian Ilsoe, Vice President, Quality and Validation Assurance, NNE A/S

Brian H. Lange, P.E., Director - Sterile and Packaging Operations Engineering, Merck & Co., Inc.

Thomas G. Lyon, Vice President Global Engineering, Bristol Myers Squibb Co.

Shinichi Osada, Chief Marketing Manager, Hitachi Plant Technologies, Ltd.

Ulrich Rudow, Vice President Worldwide Engineering and Real Estate, Johnson & Johnson

Ronald Trudeau, Vice President - Facilities Engineering Services, Baxter Healthcare Corp. 

Vetter Pharma-Fertigung GmbH & Co. KG

A Vetter World for Aseptic Processing

When Vetter Pharma-Fertigung GmbH & Co. KG – a contract manufacturer specializing in aseptic pre-filling of pharmaceutical and biotech products – needed an innovative design for its new Ravensburg, Germany facility, it did not have to search far for the best architect.

Vetter decided to use their in-house expertise in pre-filling to draw their own blueprints for the structure and equipment of their new facility Ravensburg Vetter South (RVS). The €100 million, 16,000 sq. m. facility is the winner of the 2007 Facility of the Year Award for Process Innovation.

The facility's production site currently has two filling lines, which will be expanded to four in the near future. One line is exclusively used for filling lyophilized/liquid or liquid/liquid drugs into dual-chamber syringes and cartridges. The other line can handle single-chamber cartridges and vials for lyophilized and liquid substances.

The site was designed to meet all of the challenges that technicians and scientists are faced with when aseptically filling syringes, cartridges, and vials. The facility features maximum automation throughout the building, from door openers to the use of a Restricted Access Barrier System (RABS) on the filling lines. Other outstanding qualities include high standards of sterility, safety, and quality; a self-sufficient production site with its own utility and power supply; unique production lines; and a capacity of 90 million units per year.



Exterior view.

Market-Wise Investment

Pre-filled administration systems – now comprising single- and dual-chamber syringes, cartridges, and vials – owe their popularity to being practical, safe, and user-friendly. They are used for a wide range of medications, from vaccines and antithrombotics, to a broad spectrum of new biotech drugs.

Pre-filled systems were launched in Europe in the 1970s and were established fairly quickly. In the US, pre-filled systems took some time to gain a foothold, but for the past five years the US market has expanded by 10% a year and showed a market size of \$16 billion in 2005.

A further increase in sales of lyophilized drugs, in particular, also is expected. Growth in the overall pharmaceutical market is due predominately to new biotech products which for the most part can only be stable in a lyophilized form.

The predicted growth in biotech products is confirmed in

a study by the market research institute IMS Health. The study describes the future development of the overall pharmaceuticals market this year. The report says that the biotech market in particular will show growth of 13 to 14 percent, in contrast to the five to six percent growth rate of the pharmaceuticals market as a whole.

With this information, Vetter is convinced that the new facility will prove to be an excellent investment.

Vetter currently occupies a large complex including offices and manufacturing lines on Schützenstrasse in an industrial park in Ravensburg. It

Continued on page 32.

Vetter Pharma-Fertigung GmbH & Co. KG

Category Winner – Process Innovation

Project: New Facility Ravensburg Vetter South (RVS)

Location: Ravensburg, Germany

Architect: Vetter planning team

Technical Building Management: LSMW GmbH and Axima GmbH

Structural Planning: Schneider & Partner Planungsgesellschaft GmbH

Size: Total 172,223 sq. ft. (16,000 sq. m.) with 31,431 sq. ft.

(2,920 sq. m.) production area

Cost: Approximately US \$134 million (€ 99.8 million)

Product: Contract manufacturing of parenteral pharmaceutical products

"The two current operational lines at RVS are unique in today's market. Each line is entirely independent of the other. They share neither air supply, equipment, nor space."



Purified water generation.

two current operational lines at RVS are unique in to-day's market.

Each line is entirely independent of the other. They share neither air supply, equipment, nor space. This means that one can continue functioning even if the other has to shut down for any given reason.

The RVS 1 line is used to fill dual-chamber syringes and cartridges, which are Vetter's own developments as well. The purpose of the dual-chamber syringe – the Vetter Lyo-Ject® – is to administer substances that need to be combined just before injecting. The substances might consist of two liquids, or as is often the case with sensitive drugs, a lyophilized

also has filling facilities in Langenargen, about 25 kilometers away.

The RVS site will both increase capacity, by an estimated 30%, and provide back-up capabilities.

"Automation to the Max" with RABS

Vetter built the RVS facility to house its state-of-the-art filling equipment. The

equipment. The



Aseptic intervention via gloves in RABS Technology.



Vial infeed via turntable.

substance and its solvent.

Entirely designed and manufactured by Vetter's own technology department (because most parts are not available commercially), the RVS 1 line is the only production line of its type worldwide, according to Vetter. The components, built in-house, include the washing machines, the actual filling lines, and the loading and unloading system for the freeze dryer.

The RVS 1 line is unique because lyophilization is fully integrated during the actual filling process. The absence of human intervention gives the advantage of allowing filling of lyophilized and liquid drugs in dual-chamber systems on the same line in-process. This process has been patented and allows large-scale filling of lyophilized substances and therefore an adequate market supply.

The two lines are equipped with the RABS. This allows one of the highest degrees of automation known in aseptic filling and hence safety from contamination. Vetter has been a major international contributor to the research and development of RABS.

The RABS filling line consists basically of an "isolator" placed within a conventional Class 10,000 cleanroom. Operators in this area wear sterilized cleanroom garments, including goggles. Robots were built to do all the "close-up" work, such as handling of the glass parts. The "isolator" is designed in such a way that any areas needing direct human intervention (e.g., for changing format parts or fixing something on a machine) can be reached using glove ports. The gloves are checked every day for holes. Sterile boxes are used to introduce parts.

In addition to a high guarantee of sterility, this also means greater flexibility in the use of the filling line. It can be used to fill product X one day and cleaned, disinfected, and reused

for product Y the next. The traditional isolator took at least one extra day for cleaning.

The filling process has been fully automated thanks to the use of RABS. Barrels, rubber stoppers, and closure parts are washed with purified water and water for injection. They are then lubricated with medical grade silicone oil and sterilized. A stopper is placed inside the syringe or cartridge, the substance is introduced into one end, and after placement of the closure, lyophilized in-situ. The closure is then sealed inside the freeze dryer and the syringe turned around to receive the diluent and sealed with a second stopper. The process is terminated by intensive quality controls, including a straight visual inspection.

Joining the RVS 1 line is the RVS 2 line. Its special feature, also unique in the world, is the ability to fill vials and cartridges on a single line. This offers more flexibility for Vetter's customers. The changeover takes only six hours, including line clearance and disinfection. Achieving this required the design and manufacture of Vetter's own freeze dryer loading system.

Vetter has even extended the automation idea of the RABS filling lines throughout the RVS. The result of this approach is "automation to the max." All areas are fully automated, from washing machines and the actual filling line, to freeze drying and even opening doors.

Equipment Innovation: Magazines and Monorails

One challenge Vetter and other syringe-filling operations face on a regular basis is the manipulation of the glass barrels for the syringes or the cartridges and vials.

To solve transportation issues in the cleanroom from station to station, Vetter devised a new magazine that allows the glass syringes to be grasped securely and transported without touching each other. A board with holes gently holds the glass syringes guaranteeing less breakage and avoiding



Automatic shuttle transportation system in cleanrooms.

Concludes on page 34.

www.facilityoftheyear.org



HEAR FROM THE WINNERS LIVE!

The 2007 FOYA Category Winners will present their winning concepts and discuss the challenges they faced at two upcoming ISPE events. Don't miss your chance to hear from these industry innovators!

**ISPE Facility Summit
2007: Innovative Ideas for
Accelerating Performance**
4-7 June 2007, Crystal Gateway
Marriott, Alexandria, Virginia,
USA

**2007 ISPE Annual Meeting:
Delivering Today, Transforming
Tomorrow** 4-7 November 2007,
Caesars Palace, Las Vegas,
Nevada, USA

The FOYA Overall Winner will be named during the Keynote session at Annual Meeting and will discuss their company's facility transformation from design to implementation, and its impact on the pharmaceutical manufacturing industry.

For more information, or to register, visit www.ISPE.org/washingtonconference, and www.ISPE.org/annualmeeting





Automatic loading of transport magazines.

scratches. The latter is vital in order to comply with high cosmetic standards in some markets.

Vetter also designed a lightweight, delicate monorail system that prevents particle formation by using magnetic rail technology to carry the filled magazines through the cleanrooms to and from the lyophilization chamber.

Built-In Flexibility and Adaptability

Flexibility and adaptability were built in to the design of the RVS site. One production room can be shut down for maintenance without affecting the work taking place on the other lines. The equipment is designed to enable a changeover from one system to the other – for instance, from vials to cartridges

The Dual-Chamber System: A User-Friendly Solution

The Vetter Lyo-Ject® allows administration of substances that need to be combined just before injecting. The substances might consist of two liquids, or as is often the case with sensitive drugs, a lyophilized substance and its solvent.

The two “components” of the drug are kept separate in the syringe or cartridge until they are used. All the user needs to do is break the seal, twist the plunger on the dual-chamber system, and inject.

This highly user-friendly system of administering a drug lends itself well to the growing segment of homecare. The lyophilization option guarantees far longer shelf life, which is particularly important for sensitive substances. Dosing is always exact, and preparing the injection is three times faster than by conventional means. In other words, it’s a lot safer and more convenient for the patient.

on the RVS 2 line – to be carried out within six hours, including line clearance and disinfection.

All basic media (such as air, water, etc.) can be adjusted remotely and flexibly, or shut off. Every area has its own supply of air conditioning, electricity, and media so that production can keep going even in the event of a power failure.

Attention was paid to ensure that production capacities could subsequently be expanded on the existing site. The building offers scope to expand production by two additional lines. RVS 3 and RVS 4 can be incorporated without affecting production. Even the auxiliary systems were planned to integrate two more filling lines.

In addition, RVS is a stand-alone facility, which can continue operating even if the power fails in the region.

Above and Beyond cGMP Compliance

As an international contract manufacturer in the pharmaceutical industry, Vetter ensures some of the highest possible levels of cGMP compliance, following guidance from the US FDA, EMEA, and the Tübingen regional administrative authority.


Vetter collaborated with the US FDA and the Tübingen regional administrative authority on the design of the complete facility and additionally adopted the Japanese standards for the licensing of drugs. These standards are especially stringent because they also include the external intactness of the syringes, cartridges, and vials as a criterion.

Products supplied by outside vendors were subjected to several standard tests, including Factory Acceptance Tests, Final Commissioning Tests, and Site Acceptance Tests.

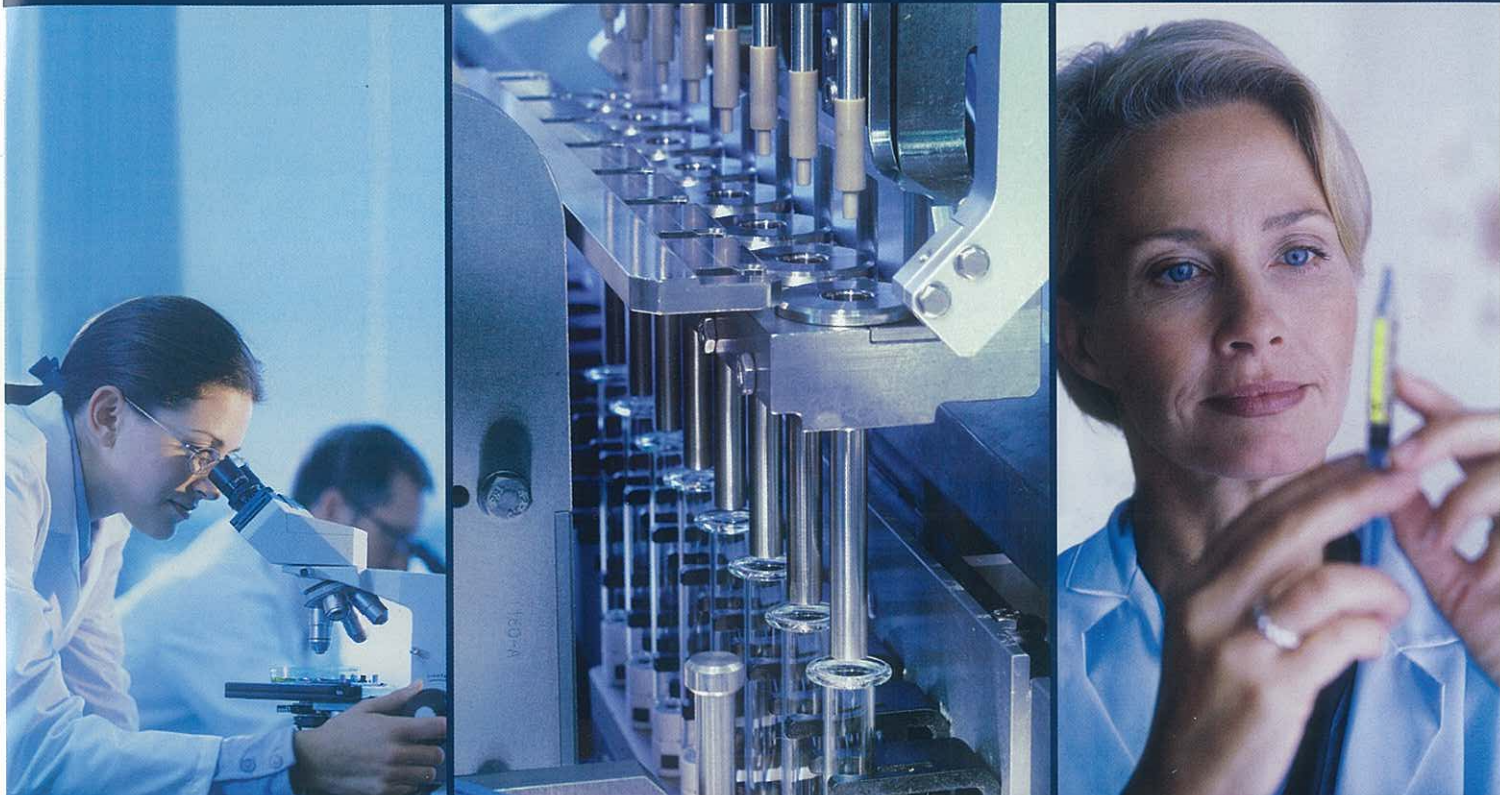
Vetter devised a GMP-compliant quality management system during the development of the RVS project to ensure product quality and fulfillment of the binding specifications issued by health officials. A high degree of automation at the facility is a central component of this system, as are the automated recording of errors and malfunctions, and the introduction of the cleanroom Class D.

Also contributing to compliance with quality requirements are the logistics concepts involving a one-way system and automatic door openers in all of Class B areas.

Vetter’s quality consciousness is further demonstrated by the fact that all pharmaceutical processes that are supposed to take place in a Class D area (according to the European Guide) are performed in a Class C environment. In other words, the company not only adheres to the legal norms, but exceeds them.

In addition to the fulfillment of 3-log endotoxin reduction requirements for primary packaging materials, all equipment and production parts with surfaces directly exposed to the product are also designed to meet 3-log endotoxin reduction requirements. All utility systems supplying liquids are electropolished. With regard to sterility assurance, all materials meet 12-log reduction requirements for bacterial endospores, once again demonstrating Vetter’s above and beyond approach to quality. 

SEE US AT: Bio 2007, May 6-9, Boston, USA, Booth # 961



Vetter Produces Quality by Design. Day by Day.

Vetter Development Service

- Development of Primary Packaging Materials
- Process Development
- Regulatory Affairs Service
- Clinical Manufacturing
- Pharmaceutical Analysis
- Transfer to Vetter Commercial Manufacturing

Vetter Commercial Manufacturing

- Fill & Finish Services
- Packaging Services
- Pharmaceutical Analysis
- Regulatory Affairs Service

Vetter Solutions

- Dual-Chamber Technology, i. e., lyophilisate/solvent, liquid/liquid
- Anti-Counterfeiting Solutions

Dosage Forms:

Syringes, Cartridges and Vials

Vetter is an independent international specialist in the production of aseptically pre-filled application systems.

Vetter provides support for its clients from the initial phases of development and regulatory approval process through to the successful product launch and commercial manufacturing.

Vetter is renowned for its quality, innovation and loyalty as a strategic partner for its pharmaceutical and biotech clients.

For US inquiries please call +1-215-321-6930.
For EU inquiries please call +49-751-3700-0.

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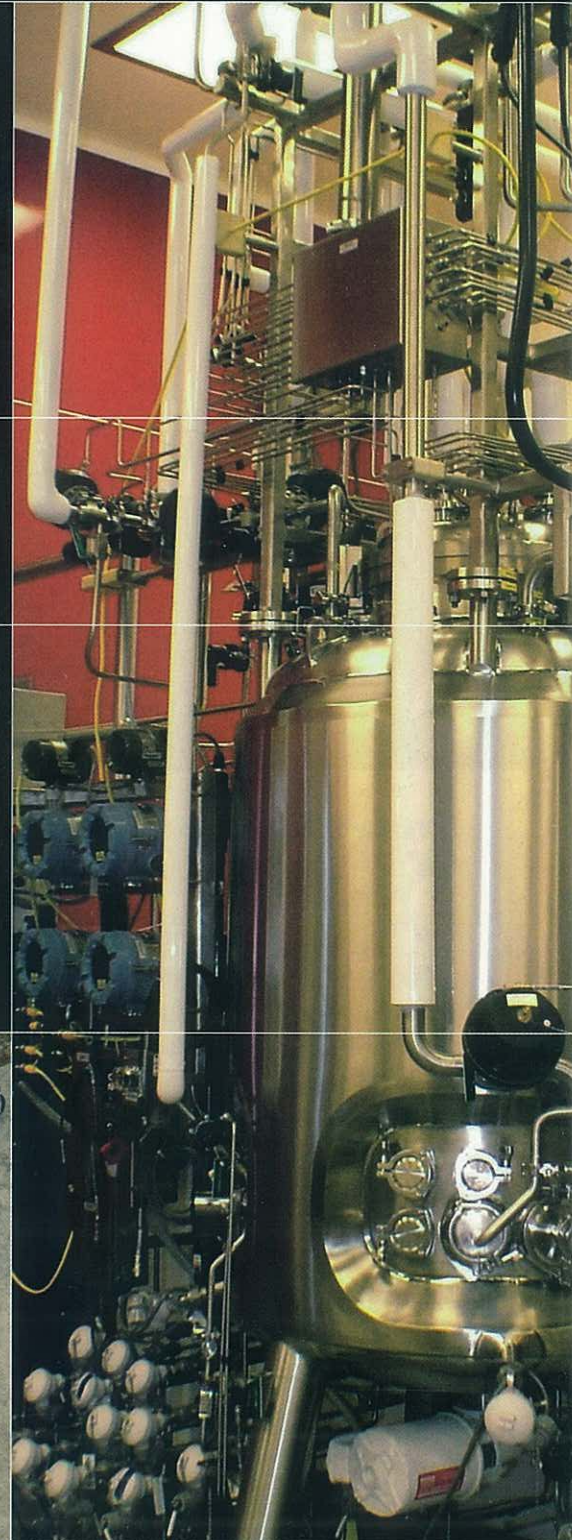
D P R C O N S T R U C T I O N , I N C .

GREAT TEAMS
build
GREAT THINGS

GREAT RELATIONSHIPS
GREAT PROCESSES
A GREAT FACILITY

DPR Construction, Inc. is proud to be a part of the Genentech Oceanside Product Operations project team.

CONGRATULATIONS GENENTECH
Winner of the Facility of the Year Award for Project Execution



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