

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

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Supplement to PHARMACEUTICAL ENGINEERING®

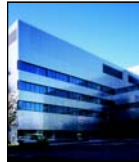


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USD to Euros conversion as of 1 October 2008.

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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

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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.

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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 Ilsoe** - 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 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 smok-



NEWCON exterior view.

ing 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.

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

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		

Deadline for
Submissions
**1 December
2008**



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.



Facility of the Year Award



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Pharmaceutical
processing

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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 as 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 coarse directly from the press in order to measure tablet

Concludes on page 8.

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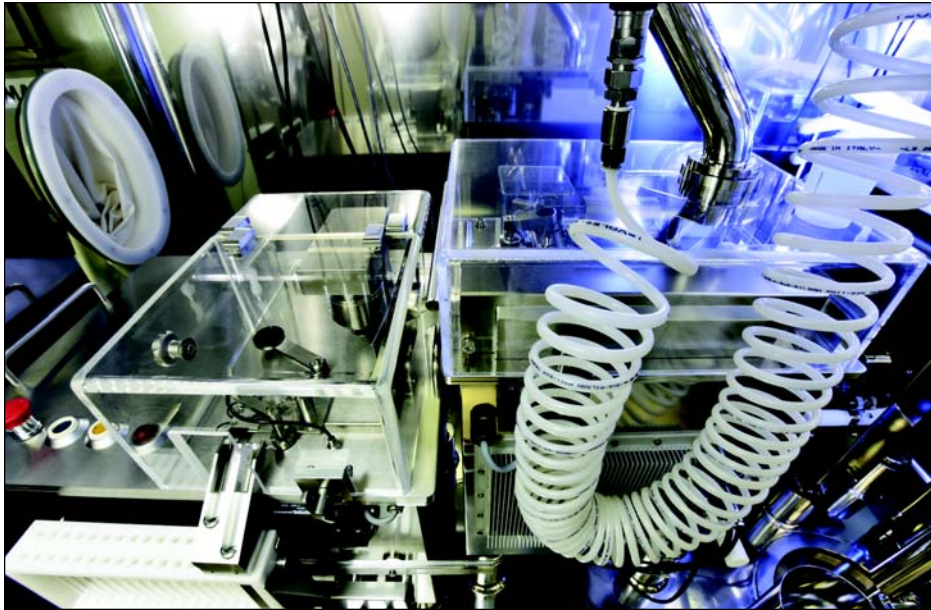


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PAT technology.



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.”

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

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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.

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		



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

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

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.

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. $10 \mu\text{g}/\text{m}^3$ (‘SMP area’).
- Two separate isolator suites for handling highly potent compounds (OEL > $0.1 \mu\text{g}/\text{m}^3$) 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. $10 \mu\text{g}/\text{m}^3$, 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. 



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

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.



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“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

Pharmacist, Bodybuilder, Nutritional Scientist?



Correct: In this picture, a pharmacist is testing the solubility of active substances. Successfully. Because the manufacturer makes exclusive use of grinding and classifying

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Isolated tablet press.

Concludes on page 16.



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**



GEA Pharma Systems

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Integrated contained high shear granulator and fluid bed processor.

- use of product thermocouples within the isolated environment
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- 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.

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.




Isolated single pot process with dryer and isolated automated sampler.

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. 



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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	Waldner Anlagenbau
EHRET Labor-u.Pharmatechnik	Gebäudeautomation	WAVE Biotech AG
Franz Ziel GmbH	The Automation Partnership	ZETA
Laservorm GmbH	LTD	

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

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.

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. 



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 can-

cer 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.

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



Biologics IV office and laboratory building.

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
Chemengineering	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

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.

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.



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Client: Roche Diagnostics
Location: Penzberg, Germany
Period: 2004 2007
Project: BIOLOGICS IV

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F. Hoffman La Roche AG – Project Execution



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.

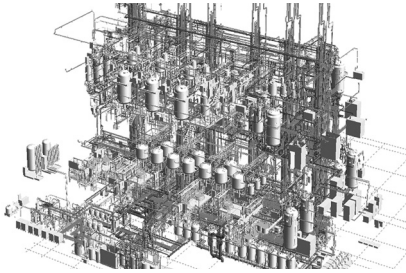
For the Cleaning and Sterilization in Place, which was critical to the success of the facility, the Users brought the practical knowledge from every day experience and the design engineers developed the system around the operative requirements. The resulting systems run efficiently.

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. 



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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

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LSMW GmbH
 Head Office
 Lotterbergstr. 30
 70499 Stuttgart
 Germany
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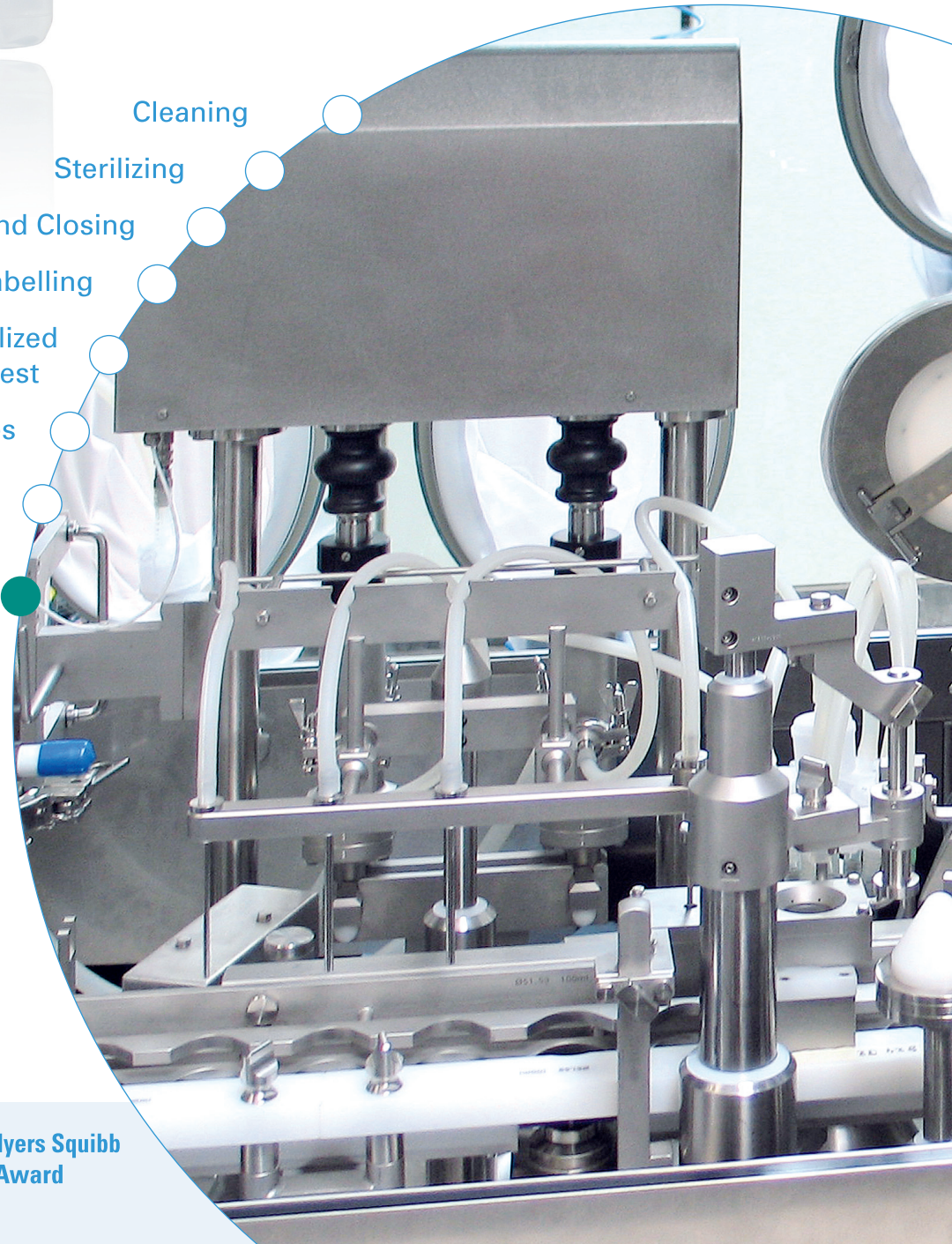


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