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GROUNDBREAKERS

Facilities & Processes Leading Pharmaceutical Modernization

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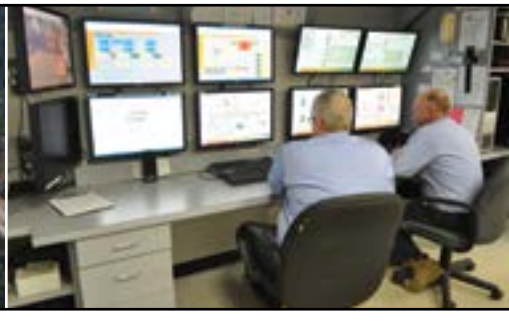
contents



GROUNDBREAKERS

FACILITIES LEADING PHARMACEUTICAL MODERNIZATION

By Steven E. Kuehn, Editor-in-Chief

Leveraging the very latest in bioprocessing technology and plant and process design, Baxter's new Covington, Ga., facility and DSM's cGMP facility in Brisbane, Australia, represent the state-of-the-art in pharma manufacturing

ASIA-PACIFIC PEARL: DSM'S BRISBANE BIOPHARMA FACILITY

One can be relatively certain that for any organization initiating and executing a project as capital intensive as building a biopharmaceutical processing facility, the strategic case for its potential return on investment must be clearly articulated as well as sustainable over the long haul. For contract manufacturing organizations serving Biopharma's growing global production capacity needs, fielding innovative, technologically advanced manufacturing assets in high-potential markets is elemental to business success.

Clearly articulating its long-term strategic and global interest in biologics, last October DSM Pharmaceutical Products, the custom manufacturing and technology business of Royal DSM, officially announced opening of its new cGMP facility for biopharmaceutical contract manufactur-

GEORGIA'S NEW PEACH: BAXTER'S COVINGTON FACILITY

Any investment in the dollars and cents world is a calculated risk. Essentially with a financial "bet," the risks and rewards often rise with the amount of capital being wagered, er, invested. Baxter International Inc. understands this and is currently making a solid bet that the global market for plasma-based therapies will create a tremendous opportunity, not only for their organization, but for the millions of people worldwide suffering from a range of chronic and debilitating immune disorders and other critical conditions.

How big is big? How about a billion dollars? In April 2012, Baxter International announced that it would be making the biggest capital outlay in its corporate history; investing a billion dollars over five years to build a state-of-the-art plasma products manufacturing facility

ing in Brisbane, Australia. Australia's Therapeutic Goods Act (TGA) regulatory agency granted the plant its A2 compliance rating, thus green lighting commercial operation. The facility was built in partnership Biopharmaceuticals Australia and some (AU) $60 million in financial backing from regional and national government agencies.

Since its opening in October, DSM has been conducting process development work and technical production runs and says that TGA-licensed cGMP production is scheduled to commence January 2014. Pharma industry analysts and financiers often find a robust supply chain of key assets analogous to a string of pearls. According to DSM, its bioprocessing pearl is contracted to serve several companies eager to be in a position to compete in Asia-Pacific market. According to DSM, "This world-class operation in the Asia-Pacific region is an important growth area in DSM's strategic development in the biopharmaceutical field." As it stands, the Brisbane facility is hosting manufacturing operations for DecImmune Therapeutics (US), RECEPTA Biopharma (Brazil) and two Australian firms, Parenta Biosciences and Opthea Pty Ltd.

A MODEL FOR THE FUTURE

"With its flexible design and use of single-use technology, the facility represents the model for the future of biomanufacturing," said Lukas Utiger, president and CEO of DSM's Pharmaceutical Products business segment at the time of the plant's opening. "It represents an important milestone in the development of Australia-based mammalian cell-based manufacturing of biopharmaceuticals, and extends DSM's contribution to the global biotechnology market." The new facility, says DSM, was designed by an expert international team of biological scientists and bioengineers, "utilizing DSM's 27 years of experience in mammalian cell culture processing to construct a purpose-built, state-of-the-art biomanufacturing facility."

DSM's new plant, at 86,000 square feet, may not be the world's largest biopharmaceutical operation, but its flexible design philosophy assures that the space provides ground-breaking levels of efficiency and capacity for each square foot. DSM says the single-use approach reduces overall operational and process costs, enables rapid product change-over and reduced batch cycle times. Product capacity is projected at 500 kg annually, with bioreactor capacity ranging from 50 to 2,000 liters.

In a recent conversation with Frank Maddalo, VP of Operations/Facility Development for DSM Biologics, he revealed that the plant's design wasn't the only thing that required flexibility. Maddalo directed the project internally and was responsible for managing the teams designing, engineering, constructing and eventually the commissioning and qualifying of the facility.

On completion, the site will contain some 1.2 million square feet of developed space including three primary manufacturing units; a warehouse; and utility, administrative and laboratory facilities.

near Covington, Ga., one ready to meet the fast-growing demand for plasma-based Albumin and IG treatments. At the time, Robert L. Parkinson Jr., Baxter's Chairman, said, "The announcement represents our confidence in the long-term global growth of our protein business."

This confidence continues to be inspired, no doubt, by the robust market potential of IGs. Global Industry Analysts (GIA) recently released a comprehensive global report revealing the global market for IGs is projected to exceed $11.8 billion by 2018, driven in part by growing diagnostic awareness and an increasing number of indications for plasma-based therapies. Currently, an industry source pegged the 2012 market value of IGs at approximately $7 billion, climbing from an estimated $5 billion in 2010.

ISPE DEBUT

Playing a key and leading role in the inception of the Covington project, Julie Kim, the global head of BioTherapeutics for Baxter, took the opportunity to debut the project to the industry, addressing the attendees of this year's International Society of Pharmaceutical Engineers (ISPE) 2013 annual meeting. In her keynote, Kim framed the business case for Baxter's milestone investment but opened with a case study describing how effective and versatile IG treatments can be. The therapeutic benefits of IG are becoming better known, and diagnostically the medical community is gaining a greater understanding of its indications and outcomes.

Maddalo, outlining the project's timeline, explains that while the deal was finalized in 2009, the project broke ground in June 2010. Construction started as scheduled, but in 2011, Mother Nature had other plans for DSM and its contractors. "In the midst of flooding in 2011, the construction site was completely inundated. It shut down the whole area for approximately a month, keeping the project shut down. We were completely over our time budget. Maddalo says quick thinking and the flexibility of the contractors on site found the solution to the loss of time was to tactically switch work from the Translational Research Institute (An element of the Australian Government's Participation at the site) to DSM's process building." Maddalo notes that in spite of this major setback, neither the schedule nor the budget took a major hit and the project proceeded as planned.

ACCESSIBLE, EFFICIENT LAYOUT

Maddalo says the Brisbane plant incorporates a variety of design strategies to facilitate operations and assure pathogen and contamination defense without impinging on accessibility by employees and customers. "One of the other interesting things we've done is we've put in corridors that traverse the bioreactor suites. We actually raised the corridor above the clean rooms. It offers a great view — you're getting a bird's-eye-view from the top down able to look into as many as eight out of the 10 areas at one time."

Flexible, single-use systems support all primary biological processing operations and are one of the defining characteristics of the Brisbane facility. Another notable layout feature is the innovative way DSM manages buffer formulation in a separate preparation suite outside its clean rooms. "That keeps the clean rooms and the bioreactor rooms relatively clutter free," says Maddalo. "You can actually run more processes and more clients at the same time in the individual rooms because they are all closed."

Heating, ventilation and air conditioning (HVAC) equipment, says Maddalo, is arrayed above the corridor and clean rooms and totally separate from the environmental controls of the laboratory. "Which makes it convenient for operations personnel, says Maddalo. "It's totally separate. It's its own independent system."

Operationally interesting is the way DSM segregates its various client's operations from one another within the facility to mitigate any chance of cross-contamination. "Instead of having a big open theater, we have closed rooms," explains Maddalo, "even though open spaces would have made operations a lot easier, with separate rooms to their process or product won't be compromised by another product or process, and you can still have privacy. But with single-use systems, there's no possibility of

Baxter broke red Georgia clay Aug. 1, 2012, for its billion-dollar investment. Here in a very familiar scene, dignitaries representing Baxter and state and local officials dig in to launch the project.

As her remarks continued, the case study served as a compelling introduction to Baxter's equally compelling business case for the Covington facility. "One way to think of plasma," said Kim, "and not everybody likes this analogy, but it's easy to understand — is similar to when you pull oil out of the ground. You can pull a number of different products out of that oil. The more products that you can pull out, the more beneficial it is …"

From a plasma perspective, she explained, one always gets Albumin, which next to IG, is one of the primary products Baxter will process at the Covington facility. Next come IGs, which are the driver of plasma fractionation volume, said Kim. Following those are a number of different plasma proteins — with a primary potential to treat rare diseases.

Over the years demand for these therapies has been increasing, said Kim. "Part of the demand growth is driven by the fact that you … have better awareness and diagnosis. Another [reason for demand growth is] one of the disease areas that we treat is primary immunodeficiency disorders. This group … represents approximately 200 or so specific disorders. Even in the United States the diagnosis rate is less than 50%, and on average it takes over 12 years for a patient to be diagnosed." While conditions indicating IG are under-diagnosed, this trend will abate, giving way to increased penetration, explained Kim, a dynamic that will generate sustainable, long-term demand globally; a macro-market force sure to drive the exponential growth in plasma protein sales over the coming years. Expansion of healthcare in developing markets will also drive growth in countries like China, a nation touted to emerge as one of the leading Albumin-consuming markets.

USA: PLASMA CENTRAL

With demand for IG and plasma protein-derived therapies expanding globally, a strategic business decision of the magnitude Baxter is making might beg the question:

people introducing contamination inside the rooms or by the way people process the work.

Certainly DSM is banking on the efficiency and flexibility of single-use systems to support the cost-efficient processing of its multiple clients at the site. However, it's widely understood that under certain circumstances, a full-on stainless steel processing train is actually a more sensible and economically feasible route to take. According to Maddalo, the second floor of the Brisbane building is open to this particular kind of thing with utilities and other elements ready to support more permanent process designs. "What we did was structurally reinforce the second floor and route utilities so if we had to put stainless steel in — at the discretion of the customer — we would be prepared. Rather than build a plant that forces everybody to run the way you want them to run, why not build a plant with the flexibility they need to do half and half, if they want to do that. If they need to do all stainless steel, they can do that as well."

BLUEPRINT FOR THE FUTURE

The Brisbane facility serves DSM's blueprint for its future as far as biopharmaceutical production for its clients. Not only does the facility field current industry standard technologies, DSM has integrated its own innovative and proprietary technologies including its XD process technology and Rhobust direct capture downstream technology. Systems that optimize bioprocess manufacturing processes; driving down cost and processing times. Maddalo says DSM's proprietary techniques and technologies can cut out several processing steps, and for that reason, earn its state-of-the-art credentials. According to DSM, its XD cell culture technology achieves 5 to 15 times higher product output than standard processes, producing very high cell densities while retaining high cell viability and consistent quality.

Offering what DSM characterizes as state-of-the-art upstream process development services, the Brisbane facility features 100% single-use upstream equipment, 250 to 2,000 liter fed batch, 50 to 500 liter XD capacity, 50 to 250 liter perfusion capabilities and advanced pre-culture/seed train that includes shake flask and wave bioreactors (2, 20 and 50 liter). Downstream, Brisbane offers customers three separate DSP suites, output up to 10 kilograms per batch, separate buffer preparation suites for crude and final fill buffers, and single-use and multiple-use Dead-End, TFF, micro and nano filtration capabilities. Lastly DSM offers column and membrane chromatography and UF/DF, VF and NFF filtration along with its Rhobust and standard clarification systems.

"Why site the plant in the U.S. when China represents such a lucrative market? According to Kim, because IG is a product based on human plasma, it's an issue of balancing supply with demand. In order to be able to manufacture therapies, explained Kim, a producer needs to have the "right" plasma available to process into IG. "The way the world works today," intoned Kim, "unfortunately the only universal plasma that is accepted across the entire globe is from the United States. European plasma is accepted in certain geographies, but the U.S. supply is the only one that's accepted universally. This represents a challenge for manufacturers in terms of being able to collect enough plasma to turn the plasma proteins into therapy."

GREEN LIGHT TO BREAK RED CLAY

Baxter's Kim explained there are many risks associated with creating and commercially sustaining such a large-scale production facility of this magnitude. Chief among them: correctly anticipating product supply and demand far into the future, staying current with advancing technologies and regulatory expectations, and operationally committing to relatively inflexible processing trains not easily or practically reconfigurable to pursue other biological products. With such a strong business case backing the project, support of both executive management and Baxter's board was earned every step of the way, culminating in the corporate decision to green light the project and begin the monumental task of matching Baxter's vision with reality.

To that end, on Aug. 1, 2012, Baxter formally broke red Georgia clay for its billion-dollar baby, beginning construction early in 2013 at a 162-acre site 40 miles from Atlanta. The campus will eventually span approximately 1.2 million square feet of developed space including three primary manufacturing units as well as a warehouse, utilities buildings, administrative facilities and laboratories.

Brien Johnson, program executive and vice president for program management, described how the plant fits into Baxter's overall production portfolio. "It really complements the network we have today," he says. "It not only expands our capacity for these products and also our plasma testing capability for our plasma collection network, but provides redundancy for a number of these operations. Today, [for] some of [Baxter's manufacturing] activities and some of [Baxter's] products we have single sources. So this will provide us with some redundancy ..." Johnson notes that Covington will eventually create jobs in Illinois because Baxter will be shipping Albumin to its Round Lake facility for fill and finish operations.

Tying all of it together, says Maddalo is a tightly integrated and pervasive automation system. For example, says Maddalo, "We have the building management control system and everything else we do while in the building goes through the server, and to the engineering department. If you're running a run, you can actually check the run, check the reactors. You can check any process through the monitoring system, which is nice as now we have all the reactors and the transfer stations, all monitored by the automation systems. This gives us the flexibility to monitor our work in the office or from home, via mobile devices. Operators welcome this ease of use, as well as someone like the site manager, who can actually check it from home or while traveling as we made sure to build in that capability." Of course, DSM maintains robust data security through a virtual private network to assure data and process information is protected.

Maddalo, along with DSM, is justifiably proud of its new Brisbane operations. "It took a lot of work. This large-scale capital project we've done — on time and on budget — it took people in Europe, Australia, U.S. and China to make this particular project a reality. A lot of work was done by virtual meetings almost 24 hours around the clock. It was also a very active engineering exercise. The team did a really, really good job." ■

GEORGIA ON MY MIND

Since the project's site selection was made clear, state and local officials have been lauding Baxter's choice and it is clear Georgia is glad to have them. "We picked the location for a number of reasons: logistics, geographic diversity compared to our other plants, the skill base of the people and the attractiveness of the site for people to relocate," says Johnson. "And the state has some great programs," he notes, "such as the Quick-Start training program. They're building their first biopharmaceutical training site adjacent to our site and helping us in a lot of different ways."

Over the last several months, construction tempo has increased significantly. By March 2014, according to a local news report, some 2,200 workers will be on site, fielded by the primary construction contractors Fluor and Turner Construction. The first manufacturing buildings are expected to be finished in 2015 with additional construction concluding in 2016.

Obviously for Baxter, the risks (as well as the potential benefits and financial rewards) associated with building a green field, state-of-the-art manufacturing and research facility were well understood. What makes Baxter's Covington Biologics Manufacturing facility a ground breaker? It's a combination of a number of things, really, ultimately a whole greater than the sum of its parts. From

ISPE FACILITY OF THE YEAR WINNERS

Groundbreakers in their own right, winners of the International Society of Pharmaceutical Engineers' (ISPE) annual Facility of the Year Awards (FOYA) program are pathfinders and innovators leading pharmaceutical manufacturing's renaissance. This year's overall winner, as well as the individual category winners, certainly maintain ISPE's tradition of highlighting the industry's best efforts. Here are the industry's thoroughbreds for 2013:

OVERALL WINNER: Novartis Vaccines and Diagnostics, for its U.S. Flu Cell Culture Facility in Holly Springs, N.C. (Winner of the Facility of the Year Award for Process Innovation.)

FACILITY INTEGRATION:	PROJECT EXECUTION:	EQUIPMENT INNOVATION:	OPERATIONAL EXCELLENCE:	SUSTAINABILITY:
Biogen Idec, for its Flexible Volume Manufacturing (FVM) Project in Research Triangle Park, N.C.	**F. Hoffmann – La Roche**, for its TR&D – Building 97 Facility in Basel, Switzerland.	**MedImmune**, for its UK Automation Upgrade Project in Speke, Liverpool, UK.	**Merck & Co. Inc.**, for its Vaccine and Biologics Sterile Facility (VBSF) Project in Carlow, Ireland.	**Morphotek Inc.**, for its Morphotek Pilot Plant in Exton, Penn.

Focused on large-scale fractionation, Covington's process galleries will look very similar to operations at its Los Angeles facility shown here.

its bank-busting billion-dollar price tag and its coming role in the biopharmaceutical revolution, to its incredibly well organized project implementation practices and sustainable operational aspects, every facet of the program is superlative in one way or another. Fueled by finely tuned Lean Six-Sigma-informed internal project management processes and organizational acumen, as well as the swagger factor gained by the architect, engineering and construction teams Baxter selected, the Covington facility is truly groundbreaking.

Here are the broad strokes framing the project. As noted, Baxter is investing more than $1 billion to establish this million-square-foot facility to support its global growth prospects with a major operation supporting plasma fractionation and purification, fill and finish and testing and R&D. Once construction and validation/commissioning are completed in 2015 and 2018, respectively, the Covington facility will have created about 2,000 new jobs across Baxter's manufacturing network.

In an interview appearing in ISPE's *Pharmaceutical Engineering*, Baxter's Kim explains that the Covington facility will be more vertically integrated than the company's other sites, combining new technologies and the best demonstrated practices from its other plants at one site. "We're adopting single-use technologies, where appropriate, to reduce contamination risk, and improve operating costs and efficiencies. The latest and emerging trends in GMP (environmental and viral) controls are also being incorporated in the facility design."

AN INTEGRAL QBD APPROACH

Baxter has taken great pains to ensure its facility will be forward leaning when it comes to overall operational and process design, innovating to strategically position the plant as a compliance leader through best GMP and QbD practices. Eric Schnake, engineering director for the Baxter Covington facility explains: "We are incorporating quality-by-design principles into the project, and it primarily starts with our validation strategy and validation master plan, which includes a number of components like process risk assessments. Ultimately, what we do in this QbD approach is identify a process control strategy — the attributes of the process that are important for quality as in critical quality attributes. We've tied that to our design and our specific equipment requirements, all of which are a very alive and thriving part of our approach here."

When fully operational, the Covington facility is projected to add up to three million liters of new capacity annually with the flexibility and infrastructure ready to

support emerging global market needs. To the executives leading this project, the intent from the beginning was always to fashion a plant that was state-of-the-art for Baxter, not necessarily the industry. Part of this attitude comes from the company's 60-year legacy of manufacturing excellence and operational experience.

What's innovative? Johnson went first, offering that "it's a couple of things; for one it's the level of automation we're incorporating into this facility, not only in process control but in the electronic batch records. We're not retrofitting a facility. We're building it with automation from the ground up." Secondly, Johnson points out that, on a humanistic level, Baxter is creating an environment that will be uniquely pleasant to the folks working there. "For example, we are making extensive use of natural light … from almost any place you'll be working, you'll be able to see daylight. Very often, facilities of this type force people into environments that are not only controlled, but closed in. I think [the design of the plant and its extensive use of natural light] will make a nicer environment for our employees."

Noteworthy also is the plant's central utility spine, a design feature mentioned by Kim in her ISPE keynote and highlighted in a later panel discussion at the annual meeting chaired by Johnson and attended by Schnake, as well as representatives from Baxter's team of architect and engineering firms. This aspect of the plant's layout creates a "super highway" of sorts for utilities and provides straightforward employee and material access to fractionation trains, fill and finish operations as well as allowing architects to segregate manufacturing from supporting operations without creating a rabbit's warren of closed interior spaces.

Schnake agrees, explaining that process and work flow attributes are better by design aiding everything from quality control to safety. "We've got some pretty robust designs in terms of facility segregation. In our business, passage and safety is a concern that we have to design around. We have built in some [relatively] unique GMP concepts around how we isolate the clean rooms. We build out progressively from that until we get to the outside." Schnake recommends likening the plant's general design to a shell: "There are layers of the shell from the outside environment down to our cleanest clean rooms — that we've baked into our design. We're also using state-of-the-art filling and isolator technologies for IG filling operations."

"This is large-scale fractionation processing," adds Johnson, and is therefore stainless-steel-centric as far as process infrastructure is concerned. "So at this scale, [process design] does not easily lend itself to a lot of disposable technologies. However, we do have some applications in the design where we are using disposable [systems] where it makes sense and where it fits with our operational needs."

We are incorporating quality-by-design principles into the project, and it primarily starts with our validation strategy and validation master plan, which includes a number of components like process risk assessments.

OPEX FROM INFORMATICS

Best practice fractionation, finishing and filling technologies, as well as defense in-depth pathogen safety principles highlight the plant's layout. But it's the highly integrated and pervasive nature of Covington's informatics and data systems which will connect the process and plant floor automation data to the back office and go a long way supporting both compliance and operational excellence. In pharma, data is everything, but its value is zero if it is not processed and disseminated correctly. "The highly integrated nature of our automation helps produce a consistent product quality — as well as enhancing our process safety, personnel safety and reducing manual operations. We want to implement an appropriate level of automation because, in the end, the manufacturing people run this process. You've got to find that right balance."

Johnson and Schnake agree there's automation that can assist you — keeping sensitive vulnerable process away from the human element, whether it's to mitigate contamination opportunities, or sparing employees from mundane, repetitive routines. But ultimately humans can't be divorced from manufacturing operations and this is what Johnson was referring to. "We try not to take the operator out of the operation. And at the same time, we want to put in the appropriate level of automation to take care of routine and actions that are repetitive. It's always a balancing act, but that's basically the goal: to keep the operator in the manufacturing process, but add the appropriate level of automation that allows him or her to monitor and still be in charge of the process." Similarly,

through robust data information handling, the data from automation can provide operators with decision support in real time. "Including the ability to historize some of that data," said Schnake, "and be available to come back later to facilitate investigations or support compliance queries."

A PART OF SOMETHING GREATER

For everyone involved at Baxter, it's immediately apparent how proud they are of this project and how motivated they are to see it to its ultimately successful conclusion. "It is pretty great," says Johnson. "I think, including myself, a lot of people — maybe nearly everyone on this program — has been attracted by the various aspects of the program." First, he explains, is the fact that Baxter is doing it to make some pretty critical drugs that help people: "Save and sustain lives, as we say, at Baxter." That's the No. 1 thing that attracts people, he says. "They're doing something that's very rewarding. On top of that, it's such a monumental project in terms of size and complexity. People see this as a really once-in-a-career type of program that they get to work on — really challenging."

To be a part of something greater like this is certainly a peak career-making experience. "This is, for sure, a once-in-a-lifetime opportunity," adds Schnake, "to be part of something this complex and this large. That's an attraction right there." But it's not the only attraction, he says. "To be building something from scratch where before there was a forest of trees — soon to become a manufacturing plant that produces a product that saves people's lives — to be part of that from the ground floor, I think, is every engineer's dream." To get involved in something like that, says Schnake, and to do it for a company like Baxter, is icing on the cake. "It's been a tremendous challenge. I'll say that; it's a labor of love is what it is. You have to work at it, but you're excited about doing it. And even when it's tough and it's hard, you still love it."

What Does the Facility of the Future Look Like?

Anke Geipel-Kern, PROCESS Worldwide

Experts all around the world are working on the future of pharmaceutical production. Gert Moelgaard, Vice President Strategic Development, NNE Pharmaplan is one of them. PROCESS Worldwide asked him about the schedule for implementation.

Mr. Moelgaard, NNE Pharmaplan is engaged in the ISPE-working group, which addresses the "GPS – Global Positioning Strategy", developing the future of pharmaceutical production. Which goals does the working group pursue?

Moelgaard: The ISPE initiative to develop a "GPS – Global Positioning Strategy" came from ISPE's International Leadership Forum, ILF, a group of industry leaders from a number of leading pharmaceutical companies around the world. ILF started the initiative because there are many challenges and opportunities for the pharmaceutical manufacturing of the future, both within manufacturing, quality, equipment and engineering that the pharmaceutical industry and its suppliers and regulators should cooperate on.

FACILITY OF THE FUTURE – MORE THAN JUST PRETTY WORDS?

What does ISPE mean with the phrase "Facility of the Future"?

Moelgaard: There are many aspects of "Facilities of the Future," both in new facilities and in upgrades of existing. For example, the need for more cost-effective manufacturing, smaller products, higher flexibility, new regulatory expectations and outdated equipment, just to mention a few. Technologies for continuous manufacturing, single-use biotech solutions, closed systems, Process Analytical Technology (PAT) are some examples.

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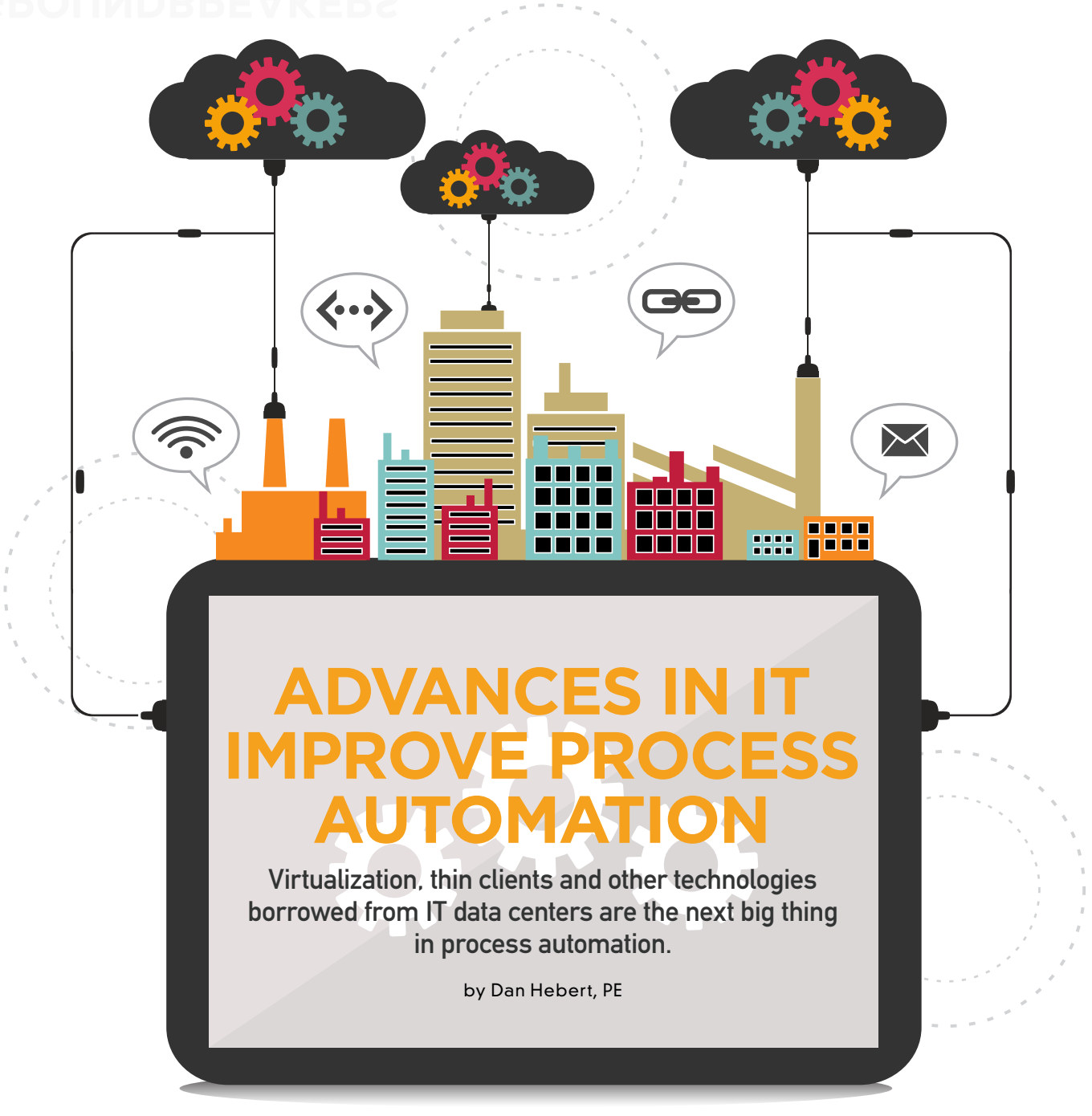

ADVANCES IN IT IMPROVE PROCESS AUTOMATION

Virtualization, thin clients and other technologies borrowed from IT data centers are the next big thing in process automation.

by Dan Hebert, PE

PROCESS PLANTS and companies adopt IT trends much more cautiously than their commercial counterparts, since safety and availability must always take priority over cost and space savings. But when new IT trends such as virtualization and thin clients promise to increase safety and availability while lowering costs, process industry firms are compelled to take a closer look.

Virtualization and thin clients were initially adopted for data centers and other commercial IT applications to save money and space. Virtualization allows multiple operating systems and associated applications to run simultaneously on one PC, so fewer PCs are required, yielding obvious savings both in up-front cost and operating costs (Figure 1), and also in reducing space requirements.

For a data center with hundreds of server-level PCs, the lower costs and space savings from virtualization can be very compelling. But for process plants, it's just not worth it to sacrifice reliability for cost savings, particularly as a typical plant has just a few PCs running server-level applications such as HMIs, historians and I/O servers.

A typical end user expresses his doubts about the benefits of virtualization. "Our process control world is many orders of magnitude smaller, more stable and more contained than the IT world," says John Rezabek, process control specialist at Ashland (www.ashland.com), a specialty chemical company. "I would most likely seek a gradual cutover for our HMIs, so we can compare reliability and performance side-by-side with one-off HMI workstations. The physical and functional redundancy of multiple independent HMIs is arguably worth what we pay for the relatively stable and reliable hardware, assuming licensing costs are roughly equal."

So the burden of proof is on the technology providers, as they must show often skeptical process industry firms that virtualization can do more than save a few bucks by eliminating a couple of PCs.

IMPLEMENTATION DETAILS

An anonymous end user at a large water/wastewater utility in Southern California shared his recent experiences with a virtualization project.

"We recently replaced eight standalone, rack-mount servers that were five years old, and due for replacement with two rack-mount host servers designed to run the equivalent of the existing system as virtual machines (VMs). There are currently eight virtual machines running on each host server in the new configuration. VMWare ESXi 5.0 (www.vmware.com) is the virtualization software, and Wonderware Archestra (www.wonderware.com) is the HMI/SCADA system.

"The following standalone machines were converted to VMs, and are each running fully redundant with the ability to have one host machine fail with no loss of SCADA functionality:

- Archestra System Platform Object Servers
- Wonderware Historian
- Domain controller
- Terminal server
- I/O servers (communications to PLCs)

"This is our first use of virtualization in a production environment, and there were no real issues encountered in the development of the virtual system. Wonderware's testing and support of their system in a virtual environment provided a solid basis for conversion, and performance is very satisfactory to date. The system has been in operation for about four months.

"As we see it, benefits of virtualization include the ability to add virtual machines to host servers to add/expand SCADA system capacity. After the existing system was virtualized, additional SCADA expansion required more Archestra System Platform Object Server capacity. The host servers were initially purchased with four CPU sockets with only two used, and with only half of the memory sockets used.

"Two additional CPUs and additional RAM were added to the host, and the SCADA system capacity was increased. There was no SCADA system downtime required since one host server hardware upgrade was performed at a time, each in a matter of hours.

"Additional VMs are being added to the hosts to provide the SCADA system Archestra System Platform Object Server capacity. Engineers continued to develop and configure the new production VMs on temporary computers, while the production hardware was upgraded. Development was not interrupted once the need for additional hardware capacity was identified.

"Virtual servers have been used in our development environment for about four years with VMWare Workstation. The development VMs run on tower servers or workstations. The VMs run development software for HMI, PLC, Historian, Reports and other applications.

"The benefits of the development environment virtualization include reduced maintenance and downtime for the development stations because new versions and patches can be applied to copies of the original VM. Old versions of programs are not lost, and new hardware is not required to keep multiple versions of programming software.

"New versions can be installed on a new VM or on a copy of the existing VM. New features of PLCs and programming software can be used more easily since additional development workstation hardware is not needed to create the new development environment.

"We are using thin client visualization in water and wastewater treatment plant environments. A recently completed project provided eight operator workstations around the plant using thin clients rather than thick client PCs as in the past. The initial benefits were greatly reduced initial cost of workstations and HMI licensing.

"On-going benefits include reduced maintenance of hardware and software on the thin clients. Thick client PCs are usually replaced every three years, but the expectation for thin clients is that they will last up to 10 years, and the thin client software technology can be supported on the hardware platform through that time period."

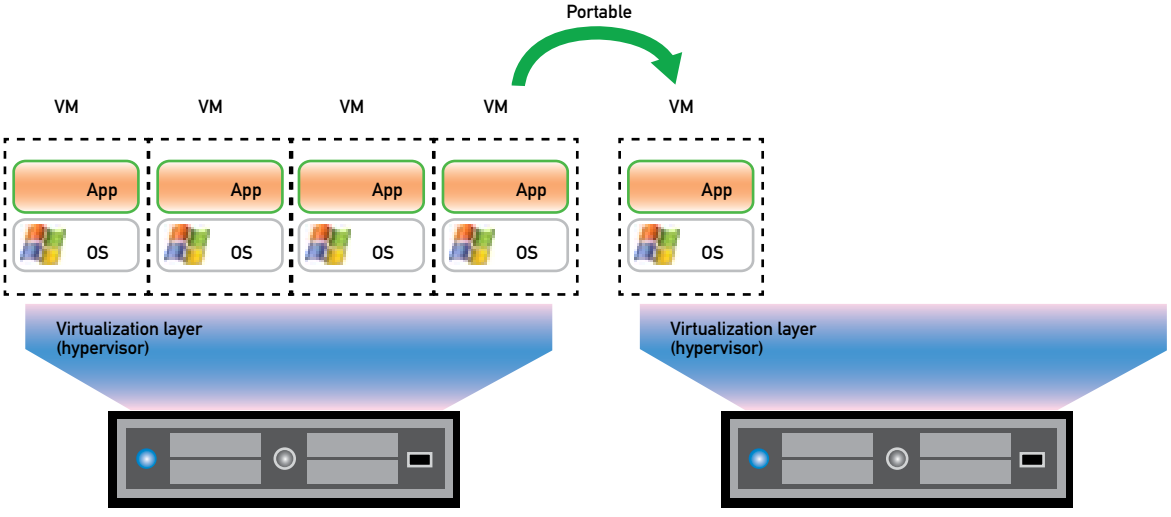

Figure 1. Virtualization allows multiple operating systems, each hosting one or more applications to run on a single PC. It also allows for easy portability from one virtualized PC to another. (Diagram courtesy of Honeywell.)

IS VIRTUALIZATION MORE RELIABLE?

It's certainly counterintuitive that putting more operating systems and applications onto a single PC instead of the old one operating system/PC model could increase reliability, but that is, in fact, the case when virtualization is applied correctly.

"For disaster recovery, since we are not using auto-provisioning (which would provide additional benefits in this area), the improvements are simply this: If we have a proper backup and a server crash, using virtual servers, we can use any brand/version of server upon which to restore the image," explains John Dage, PE, the technical specialist for process controls at DTE Energy (www.dteenergy.com), an electric utility.

Without virtualization, a server crash could be much more problematic, as it would require the replacement of the server with a new PC. The new PC would need to have the same operating system as the older model, which could be a major issue depending on the vintage of the older operating system. Even if the version of the operating system wasn't an issue, the configuration of the operating system could be, as server-level applications generally require custom configuration of the operating system.

"Traditional non-virtual ghost images required lots of hands-on work to deal with incompatibility of firmware and peripherals. Virtualization takes that out of the picture," notes Dage.

Simply put, an operating system and its associated application can be easily mirrored on a second PC in a virtualized environment, and this mirrored instance can be brought online immediately. Even without real-time mirroring, recovery from a PC failure is much quicker with virtualization.

Mallinckrodt LLC is the pharmaceuticals business unit of Covidien (www.covidien.com), a global healthcare products company. Mallinckrodt is the world's largest supplier of both controlled substance pain medication and acetaminophen. "When a PC fails, the average time to rebuild a PC has been eight to 10 hours, but the worst case with virtualization is 30 minutes," notes Tom Oberbeck, a senior electrical engineer at Mallinckrodt.

So reliability is increased not by reducing potential PC failures, but by making recovery from a failure much quicker and simpler. Users can afford to purchase more expensive and more reliable server-class PCs with features such as redundant power supplies and hard disks because there are fewer PCs to purchase, further increasing reliability.

"With virtualization, redundant servers connected to redundant storage area networks that host virtual machines can provide hot-swap fail over capability. If the primary host machine fails, the virtual machines are moved to the secondary host machine on the fly, without interruption," observes Chuck Toth, an MSEE and a consultant at systems integrator Maverick Technologies (www.mavtechglobal.com).

Increased reliability is one of the leading benefits of virtualization (others are listed in Table 1). Chief among these benefits is longer lifecycles for applications, a major boon for process industry firms.

LIFE EXTENSION

A major complaint about using PCs in process control applications has been the relatively short lifecycles of operating systems as compared to software applications. For example, an HMI application configured to run on a PC could have a lifecycle of decades, whereas the underlying operating system lifecycle would typically top out at about five years. So a PC failure 10 years into the life of an HMI application would require a new PC with a new operating system, and often major changes to the HMI application. But with a virtualized environment, the lifecycle of the machine no longer depends on the hardware and the operating system, but instead depends on the lifecycle of the hypervisor, which is typically much longer than that of an operating system.

The hypervisor is the software that runs between the PC and the operating systems on a virtualized PC, and it abstracts the PC hardware from the operating system and the application. This is what allows operating systems and associated applications to be moved so easily among PCs in a virtualized environment, whatever the vintage of the PCs.

"With the relatively quick lifecycles of PCs and operating systems compared to the long lifecycles of industrial automation installations, the hardware independence offered by virtualization is very attractive," says Paul Darnbrough PE, the engineering manager at KDC Systems (www.kdc-systems.com).

In the pharmaceutical industry, replacement of a PC is an event that requires revalidation, upping the cost to astronomical levels. Genentech (www.gene.com), a biotech company based in South San Francisco, Calif., specializes in using human genetic information to develop and manufacture medicines to treat patients with serious or life-threatening medical conditions.

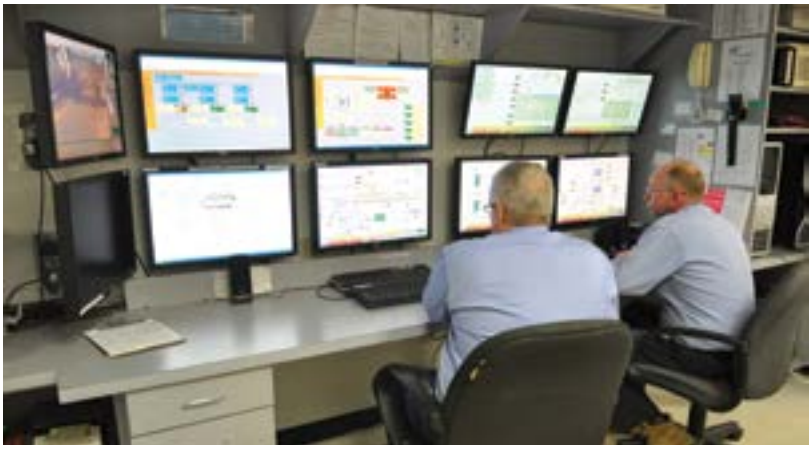

Figure 2. Virtualization can reduce the required number of PCs by 50% or more, while still providing all of the functionality of a traditional system, including multiple simultaneous views into various applications.

"Genentech estimated that the costs to upgrade one of its Windows 95 PC-based HMIs to a Windows Server 2003-based system would be approximately $40,000," recounts Anthony Baker, PlantPAx characterization and lab manager at Rockwell Automation (www.rockwellautomation.com). "Final figures topped $100,000 because of costs associated with validating the system for use in a regulated industry," adds Baker.

"Assuming that the operating systems are updated about every five years, costs quickly become a limiting factor in keeping an installed base of PCs up-to-date. Additional factors like computer hardware changes also contribute to the cost of upgrades, as each change incurs engineering expenses and possibly production downtime," notes Baker.

Instead of investing in costly hardware and software upgrades, Genentech implemented virtualization.

According to Dallas West, the cell culture automation group leader at Genentech, one of the most lasting effects of virtualization is that it allows legacy operating systems, such as Windows 95 and Windows NT, to be run successfully on computers manufactured today. This extends HMI product lifecycles from five to seven years to 10 to 15 years and possibly longer.

"Having the ability to extend the useful life of a computer system allows a manufacturer to create a planned, predictable upgrade cycle commensurate with its business objectives," West says.

"No longer is a business forced to upgrade its systems because a software vendor has come out with a new version. Upgrading systems can once again be driven by adding top-line business value, and by choosing to upgrade only when new features become available that will provide an acceptable return on investment." he adds.

Extending the lifecycle of an application cuts costs, and increasing reliability saves money by avoiding downtime. But the most direct cost savings of virtualization are found by simply reducing the number of PCs (Figure 2), while maintaining all of the functionality of a traditional one operating system/PC configuration.

AND IT'S CHEAPER

A pharmaceutical application puts some hard numbers on savings realized by virtualization. "Gallus BioPharmaceuticals (www.gallusbiopharma.com) and Malisko Engineering (www.malisko.com) recently deployed a new Rockwell Automation PlantPAx process automation system that replaced six non-virtualized servers with two virtual servers, saving 60% of the server costs, or $20,000," says Steve Schneebeli, the lead systems engineer at Malisko Engineering.

Similarly, Mallinckrodt saved big on a recent central utilities upgrade project by using virtualization to reduce the required number of PCs from 22 to just 13 physical PCs and 9 virtual machines. "Upgrading the current existing applications on the 22 PCs was significantly more than the cost of the entire new VM infrastructure. Virtualization produced an initial cost avoidance of $120,000, and a future projected cost avoidance of an additional $100,000," says Mallincrodt's Oberbeck. "We anticipate reduced downtime when dealing with production issues, and when making process improvements. Maintenance costs will be cut, and there will be substantial energy savings."

Fewer PCs also means less points of entry for hackers and other intruders, reducing costs of compliance, and making it simpler to secure the system. Most all virtualized systems are housed in secure, protected and climate-controlled locations, but many users require access to the applications running on these systems from the plant floor or the field, which is an area that's a great fit for another data center technology—thin clients.

THIN CLIENTS

When users want to access virtualized systems, the two main choices are PCs and thin clients. For offices and other protected environments, PCs are usually the best choice because in most cases the PCs will be used for other tasks in addition to process control and monitoring.

But on the plant floor and in the field, thin clients have a number of advantages over thick client PCs (Table 2). "The beauty of thin clients is that, if the operator console fails, it can be swapped out in minutes. Once reconnected to the virtual machine, the operator picks up where he or she left off, saving hours of precious time," explains Maverick's Toth.

A recent pharmaceutical project realized a cost savings of 33% and a footprint reduction of 50% by using thin instead of thick clients. "With thin clients, users can create 'follow-me' operator workstations that can follow a single operator from thin client to thin client in a large plant, instead of creating a thick client at each physical location," explains Schneebeli of Malisko.

TABLE 1: VIRTUALIZATION BENEFITS

1. Increased reliability through faster recovery
2. Simplified hardware upgrades
3. Can move existing applications among PCs with no downtime
4. Can add applications with no downtime
5. Longer application lifecycles
6. Can create new instances based on existing instances
7. Fewer PCs required
8. Takes up less space
9. Reduced energy consumption
10. Improved security

TABLE 2: THIN CLIENT ADVANTAGES OVER PCS

1. Software maintained at the host
2. Longer lifecycles
3. Improved security
4. Reduced upfront and total lifecycle cost
5. Smaller footprint
6. Easier to deploy in harsh environments
7. Each station can support multiple functional users
8. Faster replacement and reboot after failure

A recently completed water/wastewater utility plant design provided eight operator workstations around the plant using thin clients rather than workstations as in the past. The initial benefit is greatly reduced workstation costs and HMI licensing.

Thin clients can be either fixed operator interface terminals, or portable wireless devices. "Virtualization provides a path to enabling workers to access their workstations on a variety of hardware platforms," observes Rockwell Automation's Baker.

"From tablets to thin clients, users can access their workstations from anywhere they have Internet access inside or outside of the plant. The desktops no longer run on the local hardware, but instead are securely running back in the data center. Users will be able to view and interact with their desktops through new virtualization desktop infrastructure products," adds Baker.

Another supplier offers a host of thin client solutions based on open standards. "We provide several workstations and panel products that include the Windows Remote Management designation for thin client virtualization applications," says Louis Szabo, business development manager at Pepperl+Fuchs (www.pepperl-fuch.com).

Its customers are taking advantage of thin-client

visualization of virtualized systems in a number of ways. "In a silicon processing application, thin clients are used in facilities monitoring water treatment and HVAC systems. A keyboard, video, mouse (KVM) extender wasn't feasible due to distances involved, and a full PC was too expensive due to hardware and software costs. Thin clients were already employed on our customer's business systems, so with the DCS vendor's recommendation, the customer decided to utilize thin clients for remote monitoring," explains Szabo.

Virtualization and thin clients are being used in many process automation applications, either together or separately. The future promises to bring these technologies to the forefront, but virtualization in particular will require a change in mindset among suppliers, system integrators and end users.

THE FUTURE

Thin clients are already in widespread use among process control plants, but virtualization is catching on more slowly, in some cases because end users and system integrators are waiting on automation suppliers. "The major HMI software vendors have begun to offer some products that are 'virtualization- ready' for a production environment within the last few years. Therefore, even though virtualization is a proven technology in the IT world, it is still fairly young in the industrial automation world," says Darnbrough of KDC Systems.

"Many of our larger and municipal customers will be slow to adopt virtualized systems in their specifications, but we anticipate starting up a cogeneration, balance-of-plant system at a major customer site this year with an HMI that takes advantage of virtualization," notes Darnbrough.

HMI software vendors and other suppliers of server-level software applications have only recently begun to offer virtualization-ready products, but their offerings are growing rapidly, and are being packaged for quick installation and use.

"Most recently, Rockwell Automation introduced virtual image templates for our PlantPAx process automation system, including a system server, operator workstation and engineering workstation. These templates are preinstalled with PlantPAx software, and are delivered as images on a USB hard drive, helping to reduce validation costs and system deployment time," explains Baker.

"Setting up and installing a complete process automation system traditionally takes several days, with various operating systems, software packages, and patches. However, with a virtual image template of each server and station, system components can be deployed in minutes. The templates are distributed in Open Virtualization Format (OVF). OVF is an open standard for distributing virtual machines, and is compatible with a number of virtualization solution providers," concludes Baker.

ABB (www.abb.com) has embraced virtualization technology for its entire server/client architecture. "Our System 800xA is factory tested and fully documented using virtualization technology," says Roy Tanner, 800xA global product marketing channel manager for Americas at ABB.

"Testing is done to ensure performance levels meet our customer's most demanding applications. Our entire automation platform can run in a virtualized environment, including redundant servers that are connected to controller networks, application servers (historians, asset optimization, batch management, etc.) and even operator clients," adds Tanner.

This is what's happening now, but what does the future possibly hold as data center technologies move to process automation?

"I anticipate three main advancements in the next 10 years," predicts Paul Hodge, product manager for virtualization at Honeywell Process Solutions (www.honeywellprocess.com). "It will be simpler to support more advanced virtualization features, such as high availability and transparent patching and upgrades. We're doing this already with our turnkey blade server offering, and easy access to advanced features will continue to evolve.

"Virtualization has abstracted users from having to deal with physical hardware, but they now need to interface with the hypervisor. Private cloud technology will gradually be adopted in the process automation industry, and will abstract users from being exposed to the hypervisor. This transformation will allow users to be more application-centric," explains Hodge.

"Finally, there will be increased use of virtual appliances, which are virtual machines containing the selected application with a bare bones and properly configured operating system. The idea is that the application and operating system are one. If the appliance needs to be upgraded, both the application and operating system will be upgraded at the same time. Users will only need to turn the virtual appliance on in the same way they would a DVD player or TV," foresees Hodge.

Virtualization and thin client visualization are growing rapidly in the process industries due to lower costs, greater reliability and longer lifecycles. Further advancements promise to increase adoption rates, propelling process automation systems to a brave new world that takes advantage of IT advances, while improving safety, availability and security.

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A Biotech Facility Transformed

In less than two years, Boehringer Ingelheim increased productivity fourfold at its newly acquired process development and manufacturing facility in Fremont, Ca.

By Ralf Otto and Frank Steinbach, Boehringer Ingelheim

IN MARCH 2011, Boehringer Ingelheim (BI) acquired an existing biotech manufacturing facility in Fremont, Ca. The decision to purchase the site was driven by three strategic objectives: to secure process development and production capacity for BI's own range of biomolecules, to extend its global biotech contract manufacturing business, and to give BI a significant presence in the San Francisco Bay area, the largest biotechnology hub in the world.

At the time of acquisition, achieving those objectives looked like a daunting challenge. The site was producing a single commercial product, but BI needed the capability to make dozens of different molecules and to meet the needs of every stage of the development process from toxicology studies and the early clinical phase onward. If the facility were to enter the highly competitive contract manufacturing space, it would also need to dramatically increase its productivity and drive out cost. Quality needed to be on a very high level, both to satisfy regulators and to ensure that products were produced right first time even in a multi product set-up.

SITE VISION

Using the strategic objectives as a starting point, and benchmarking Fremont against the best in the world, the site leadership team developed an ambitious vision for the facility. They started with targets for just five key performance indicators: productivity, on time delivery, right first time, ramp-up to multiproduct capability and a measure of staff mindsets. If the metrics were straightforward, however, the targets certainly were not.

For the leadership team, the transformation effort wasn't just about meeting business objectives. The team wanted Fremont to become a shining star in the BI portfolio and the targets reflected that aim, including a threefold improvement in productivity, for example, and a 50% reduction in production deviations. The time frame was challenging, too: BI aimed to hit its targets within 18 months, while simultaneously making the changes needed to integrate the site into the systems and processes of the wider BI organization, as well as phasing out all

infrastructure provided by the previous owner.

To achieve what BI had to do in the time available, the site leadership team designed the transformation effort in two phases. The first phase would deliver a rapid and significant improvement in both performance and staff mindsets, by making the most important, but sometimes painful, changes to the way the plant was operated and managed. The second phase would be about sustaining continuous improvements over the long term, and building world-leading capabilities at the site.

Critically, companies in the BI network assigned some of their most important biotech development and manufacturing projects to the site, and the site was also successful in quickly acquiring external contract development and manufacturing deals. The steep learning curve in operational execution and positive client feedback from these projects helped the site to gain confidence in its vision and ambitious targets.

At the end of every shift, BI introduced a daily performance dialogue among shop floor teams.

FAST, PHASED CHANGE

For the initial phase of the transformation, the site established a steering committee to drive the change process. They knew that whatever changes were made at Fremont would need to be aligned with the wider BI organization, so that committee included representatives from the Global Operations, Quality and Process Sciences functions. The change effort began with a detailed diagnostic of the site. Working with a group of external advisors and biotech experts from within BI, the leadership team spent two weeks examining every aspect of the plant's operations in order to find opportunities to eliminate waste and improve performance. The diagnostic team's deep understanding of the unique challenges of biotech production helped them produce hundreds of improvement ideas in that time, with many suggestions also coming from their own staff.

OPERATING IMPROVEMENTS

About 200 of the ideas identified in the diagnostic process were "quick wins," changes that cost little to implement, but could deliver substantial improvements on the ground. For example, BI replaced complex pipe jumpers comprising more than 17 components with a much simpler, three-component design. The new design meant reconfiguring connections, which went from a three-hour, two-person job, to a task that took a single operator less than half an hour. Similarly, the introduction of automated small parts washers meant that instead of requiring four people to manually clean components between batches, operationally the facility needed only one.

Making these changes quickly didn't just give them immediate performance improvements, it also sent a powerful signal to everyone in the plant that BI was serious about the change process, and that the organization was ready to listen to their ideas and invest to put them into action.

After 'wave zero' of rapid improvements, BI started implementing the hundreds of detailed changes that would take the plant to where the company needed it to be. Those changes took place in three subsequent waves of about two months each. Each of these waves was designed to be broader in scope and the number of participating staff than the last. The team started by looking for improvement opportunities within individual functions, before moving on to examine cross-functional interactions, and finally to improvements in the way the plant interacted with its customers and the global BI organization.

The changes made during these phases were profound. A key focus, for example, was in reducing the cycle time to deliver a complete batch of product. By adopting a more aggressive approach to batch scheduling, improving the training of production staff, reducing unnecessary waiting time between steps and by implementing some key technical changes, like the introduction of faster in-process sampling technologies, BI found opportunities to reduce overall cycle time in downstream processing from 23 days to less than a week.

PERFORMANCE MANAGEMENT

In any effort to transform the performance of a site, technical changes, whether to equipment or processes, are only one part of the story. The facility could only perform to its full potential if BI's people were enabled and incentivized to perform to their full potential. Recognizing this, BI designed and implemented a completely new performance management system for the Fremont facility.

Starting with site level KPIs, the leadership team developed metrics and targets for each function, which in turn cascaded down to shop floor-level metrics. Again, BI maintained its emphasis on simplicity and relevance, with only 12 site-level and 12 functional KPIs. The leadership team made sure all of its metrics were highly visible, too,

with a site-level dashboard that was regularly reviewed by the team, KPI boards for each function outside the office every functional leader, and shop floor performance boards displayed in team rooms.

At the end of every shift, BI introduced a daily performance dialogue, in which shop floor teams assess their own performance against their targets, identify the root cause of any deviations from the required performance and agree on actions to tackle those root causes. Responsibility for ensuring the implementation of each agreed action is allocated to a single individual, with an agreed time frame for completion, and their progress is monitored at subsequent daily meetings.

MINDSETS, BEHAVIORS AND CULTURE

The final essential element of our transformation effort involved the mindset and attitudes of the facility's staff. When BI acquired the Fremont site, the company was the third owner in five years. Interviews and focus groups with frontline staff showed that, while they were passionate about their roles, many were struggling to find direction, or felt overwhelmed by the work that needed to be done. If the effort were to succeed, it was vital that the site leadership bring the staff's hearts and minds along with it.

BI's program to change mindsets and behaviors had four elements:

- First, an extensive internal communications campaign, which gave staff regular updates on the changes being made, and why they were essential if Fremont was to become a more flexible, versatile and globally competitive site.
- Second, BI invested in capability building, so that people received the training, coaching and support they needed to do their jobs to the very best of their ability.
- Third, the site leadership introduced a regular survey of staff attitudes and concerns, which gave invaluable insight into the morale of the whole organization, and allowed site leadership to tailor communications and training efforts to meet emerging needs.
- Finally, to reinforce the commitment to making the site the best of its kind in the world to work in, leadership made significant changes to the interior of the facility, with new colors, updated furniture and signage, and improved open-plan offices and meeting areas.

To really believe that the organization is committed to improvement over the long term, people need a clear demonstration of that commitment from management. To this end, all managers at the plant, from the senior team down, were encouraged to take an active role in improvement activities. Managers attended daily review meetings, participated in problem-solving sessions, coached team members and rewarded good performance in a highly visible manner. This was a totally new way of working for many managers, but most found it a stimulating and rewarding change.

In particular, a small group of key staff were enthusiastic "early followers," understanding clearly the need for change, embracing the methods required to deliver it and acting as advocates for the transformation process wherever they went. These half-dozen individuals became a driving force in the transformation, helping the effort to gain vital traction during its early stages.

Not everyone found the transformation as easy to understand or accept, of course, but at every level in the organization, people who found it hard to adapt to the new business direction were not permitted to slow down the improvement process. Ultimately, if they could not alter their ways, the organization found alternative roles for them, or removed them from the organization.

OUTCOMES

Two years after this journey began, the results speak for themselves. Fremont has been transformed from a mono-product to a multi-product facility. Higher demand and a highly engaged workforce mean output per worker has increased fourfold compared to 2010. The site's historical attrition rate of 10% has dropped to below 2% for the last

six months. Quality has improved significantly as well: To date, 25 regulatory and client audits have been successfully managed with no critical observations. An FDA inspection in 2012 produced the excellent result of zero 483s.

BI Fremont is also meeting its business goals. Since March 2011, the site has secured more than 10 development and manufacturing agreements with internal BI partners and external clients, and more are in the pipeline. Commercial offerings are broadening too, with investment in new technologies, like single-use bioreactors and disposable flow path purification. The site's manufacturing and process sciences facilities, given their uniquely transparent design, have been used by local biotechs, universities and legislators for tours, events and conferences to see the inner-workings of a state-of-the-art biotech facility in action.

These results are only the end of the beginning, however. BI site leadership is now well into the second phase of the transformation effort, with the emphasis moving from the radical changes of the first 18 months to building a culture of strong, sustainable, continuous improvement. Even more significant is the change in ownership of the second phase of the program. While the first phase of the transformation was necessarily imposed from the top down, with the use of considerable external support and expertise for the first six months, the current phase is very much a homegrown effort, designed, managed and implemented by BI Fremont's staff. Given where the site was two years ago, this is a remarkable testament to the willingness, enthusiasm and skills of the staff and the effectiveness of this ambitious transformation program.

The Pharmaceutical Facility of the Future

Smaller batches, lower costs, increase quality

The need to improve agility and reduce financial risk is driving new approaches to plant design and operation, and the use of new technologies.

For years, observers have said that pharmaceutical manufacturing must become more flexible and must change the way it handles R&D and manufacturing. During the last decade, facilities have not become automated, PAT and QbD have not started a revolution, although they are gradually being applied.

U.S. discussions of healthcare reform may result in higher production levels and lower drug prices. The approval of follow-on biogenerics may shave years off the marketable life cycle of biotech drugs.

Bob Bader, senior manager of technology for pharma and biopharma at Jacobs Engineering (Conshohocken, PA), says, "We don't need that much product anymore. We're not talking about 2000 kilograms, but 200 to 300 kilograms per year." Therefore, the upstream portion of bio facilities has become smaller and 100% single-use equipment becomes possible. "It gives you a lot of flexibility but also simplifies design, automation and fixed capital costs," he says. This thinking may drive less-expensive, more flexible pharmaceutical plant designs.

Bader's colleague, Deepak Agarwal, director of pharmaceutical technology at Jacobs, sees pharma engineering projects aiming to:

- Minimize the cost of goods and the total installed cost
- Further accelerate scheduling for design, build and construction
- Make facilities more flexible and adaptable for a range of products
- Continue to make high-quality product

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