WWW.PHARMAMANUFACTURING.COM

Pharmaceutical MANUFACTURING

THE DRUG INDUSTRY'S VOICE FOR MANUFACTURING EXCELLENCE

PutmanMedia®

SHOW ME THE MONEY

Pharma's Facilities & Operation Investment Research Results

NEXT PAGE ▶

PROCESS AND FACILITY DESIGN FOR A MONOCLONAL ANTIBODY FACILITY

SINGLE-USE TECHNOLOGY DELIVERS STRATEGIC FLEXIBILITY TO EMD MILLIPORE

BY CHRISTIAN CATTARUZZA & SEBASTIEN RIBAULT, MILLIPORE S.A.S., FRANCE

THE BIOLOGICAL drug products market is expanding, especially in emerging economies. With the improvement of living standards in those countries, the number of patients accessing drug treatments is growing rapidly. In Brazil alone, an estimated 40 million people joined the middle class between 2000 and 2010. In China rapid economic growth and the emergence of a middle class with growing disposable income in the last decade have contributed to an increased demand for high-quality healthcare services. In India the number of middle-class households (earning between $4,413 and $22,065 a year) is estimated to increase more than four-fold, from $32 million in 2010 to $148 million by 2030.

Countries that are growing in size and wealth are looking to establish more domestic industries to support a growing population that can afford to buy more goods and services. In particular, government-driven incentive programs are multiplying to encourage local investments in biologics production facilities. For example, if a company in Brazil decides to build a modern manufacturing plant to produce a product for the local market, the government will buy this product from the company. Companies that do not have plants in Brazil will eventually be eliminated from the market for a particular product. In India the government has been proactive and supportive in driving the growth of the biotechnology sector by offering grants and tax incentives, and implementing investment-friendly regulations.

Since the mid-1980s, South Korea is by far the best example of government support for the biotechnology industry. One of the fastest-aging countries demographically in the Organization for Economic Co-operation and Development (OECD), South Korea needs to prepare for and deal with the rising incidence of chronic diseases such as diabetes, Alzheimer's and Parkinson's. The government provides various incentives such as tax reductions or cash grants to companies targeting treatment of those specific diseases.

In other cases, governments apply a protectionism strategy favoring a model where drugs must be produced locally to be eligible for local healthcare system reimbursement or to be available for patients. In Russia, for example, local pharmaceutical companies are able to meet only a small percentage of the country's requirements and 80 percent of drugs are imported. To change this situation, Russia is implementing extreme protectionist policies such as a law that allows discriminatory procurement practices by giving the government the right to enforce a ban on foreign goods in public procurement tenders.

At the same time, some biologics blockbuster patents going to public domain lead to development of multiple biosimilar programs, benefiting the broader population with lower treatment costs. With more than 200 biosimilar drug development programs — spanning from research to Phase III — in China, Brazil, India, Turkey and Russia alone, biosimilars are becoming a public health challenge and a large business opportunity in many countries.

This overall situation is leading to a new "for country in country" strategic trend in biopharmaceutical industry supply chains where biopharmaceutical companies are considering localizing small scale production facilities to serve specific countries or regions.

However, there is a high level of risk related to investments in emerging countries. Political instability can be of great concern in some countries, turning a winning market environment into a real no-go in a matter of months. Economical fragility and a government's inability to fund existing incentive programs often limit attractiveness of those markets. Also, the limitation — or absence, in some cases — of healthcare systems, as well as relative complexity of drug reimbursement processes may limit populations' access to drug treatments.

Figure 1. The design of Flexware assemblies assures correct installation every time.

Companies interested in investing in biologics in emerging countries such as Brazil, Russia, India, China and in middle-eastern and Asian-Pacific countries must solve an equation which consists of investing quickly to be the first to enter, lowering the financial risks and ensuring drug products cost of goods sold (COGS)are competitive and affordable. The key to this equation is the flexible factory concept.

The flexible factory concept is a single-use facility designed with ease of use, minimized contamination risk and flexibility in mind. A wise implementation of single-use technologies allows drug manufacturers to get the best possible outcome from those technologies: easy and fast re-purposeability for a variety of processes, increased capacity with rapid changeovers between batches, minimization of SIP/CIP steps with associated time and costs savings. The ability to run some of the process steps closed and continuously also allows fewer cleanroom classifications and reduced capital expenditures while increasing facility flexibility and adaptability to meet local market demand.

Despite the introduction of single-use new technologies, the majority of biotech processes and facilities still contain a number of stainless-steel and multi-use equipment. At EMD Millipore, a subsidiary of Merck KGaA, Darmstadt, Germany, the company made the decision to move away from this traditional setup and implement full single-use processes at both the laboratory and manufacturing scale. This change from multi-use to single-use was developed in parallel with the revamping of EMD Millipore's Biodevelopment Center in Martillac, France, as well as part of the company's global strategic development of flexible facilities concepts.

ALL STEPS UP, AND DOWN STREAM

With the adoption of single-use equipment, all steps from upstream to downstream and fill and finish can be completed in a single-use manner. This is not only true for small and medium scale; large scale disposable systems are now available on the market and routine manufacturing can be done using disposables as well. EMD Millipore's implementation of disposables is going from development scale to routine manufacturing at the 2,000 liter scale.

EMD Millipore has seen a number of advantages to implementing single-use equipment including reduced risk of contamination, ease of use and enhanced flexibility. The risk of contamination is reduced at all steps as the disposable systems arrive sterile with no need to clean or sanitize, and are set up for the run without opening. As an example, bioreactor bags are connected to media bags through sterile connectors so there is no open phase and the harvest is completed the same way. Welders can be used as well, depending on the scale.

Ease of use is threefold. First, operators require less training than with stainless-steel equipment (less piping,

The flexible factory concept is a single-use facility designed with minimized contamination risk and flexibility in mind.

no spare parts, no cleaning or sanitization, etc.). Second, the assemblies used on the hardware part are typically preconfigured for simplified installation (connectors with "two clicks" confirm good connections, asymmetric pieces avoid bad orientation, etc., Figure 1). Finally, operations are mostly automatic and the recipes used are virtually foolproof.

In terms of enhanced flexibility, EMD Millipore has found implementing single-use equipment to yield a range of advantages. For one, bioreactors are no longer fixed; they can be moved from one room to another depending on needs. Downtime is reduced to a few hours rather than several days, as is the case with stainless steel. When running a single-use upstream suite, drug A can move from one bioreactor to three in parallel for the validation runs of drug B in less than a day. The ability to reconfigure in a day or less provides superior flexibility and allows quick changes in production plans.

Buffers are prepared in single-use mixers and then pushed into the suite for use. As nothing is fixed, there is no need for hard piping and maximum flexibility in the options. A new buffer can be brought in or taken out without impacting the suite and the rest of the process.

New generations of equipment, such as the Mobius' FlexReady System, make it possible to have one piece of equipment for several operations. The tubing has been replaced by a new type of consumable that prevents operator errors (Figure 2). These systems enable either chromatography or TFF with a single piece of equipment. The additional cart will contain pumps for chromatography or a tank for TFF. This new concept not only reduces footprint, but also investment and operator training. Flexibility is embedded in the equipment design. All of this equipment can be connected using sterile connectors or welders, making running a closed process now feasible.

IN THE BAG

Instead of using a vial, cells can be stored in a bag at -80°C or in Nitrogen. This bag is connected by welding to the first seeding bioreactor and cells are transferred by gravity. Cells are grown to the desired concentration and transferred again by sterile connection to the next bioreactor and so on until the production unit. The next steps through clarification are similar and the resulting clarified harvest is collected into a closed bag.

Purification can also be performed in a closed and continuous manner using several columns consecutively loaded, washed, eluted, cleaned and regenerated. Virus inactivation happens in a closed bag between protein capture and a series of membrane absorbers. The process ends with virus filtration and aliquoting.

This closed process has several advantages, including reduced risk of contamination and the ability to run a multiproduct facility with ballroom suites for upstream and downstream or several products in the same area. These benefits are creating a clear global trend toward single-use equipment and flexible facilities concepts.

THINK CAPITAL UPGRADE

When you think equipment, think Federal Equipment

We sell high-quality machinery
We buy surplus equipment

OPTIMIZE YOUR CAPABILITY

When you need to upgrade your facility or reduce the risk of equipment failure, Federal Equipment gets you online with the right machinery in the shortest time. As a trusted source of processing equipment for over 50 years, we have extensive industry expertise and a vast inventory viewable in pharma-dedicated warehouses.

Federal Equipment Company

WWW.FEDEQUIP.COM
+1 877 536 1538
For more information, email us at pharmaceutical@fedequip.com

JANSSEN EMBRACES CONTINUOUS MANUFACTURING FOR PREZISTA

STRATEGY SEEKS CM'S WELL-RESEARCHED SAVINGS AND EFFICIENCIES FOR ITS GURABO, PUERTO RICO, PLANT

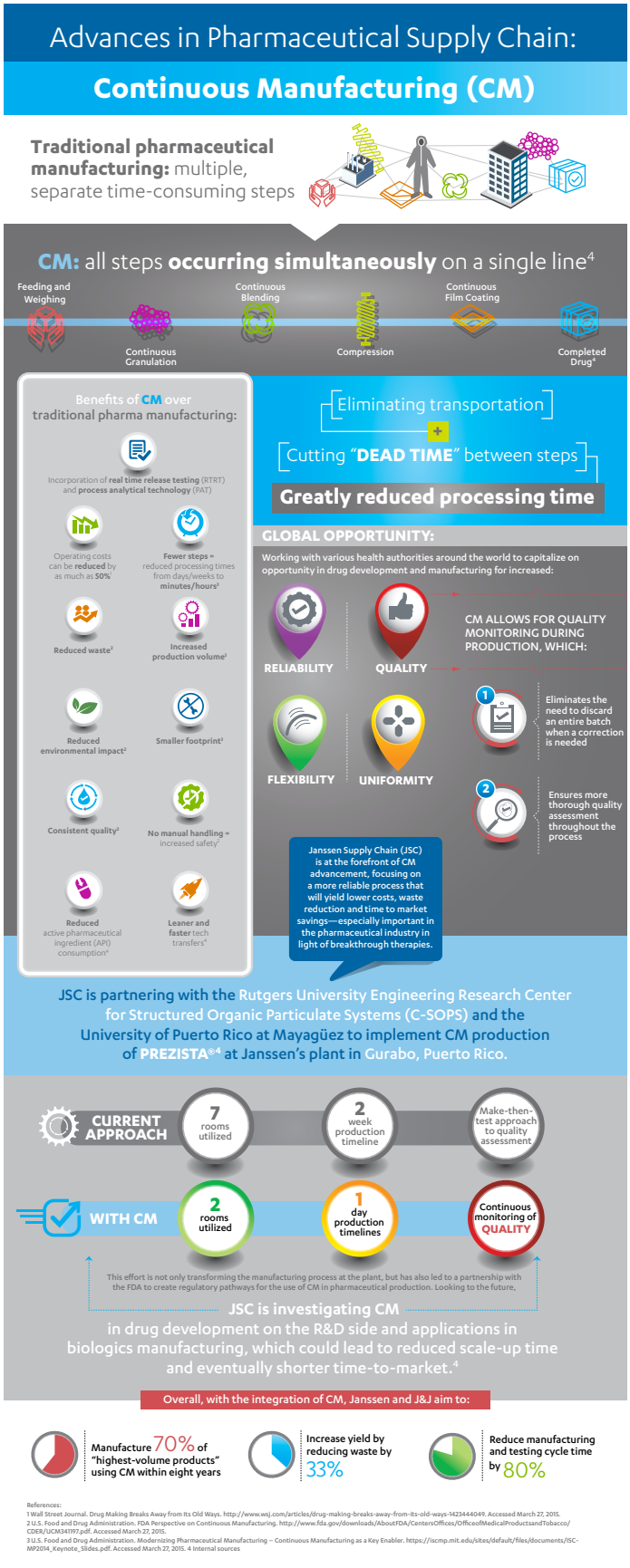
BY STEVEN E. KUEHN, EDITOR IN CHIEF

JANSSEN AND its corporate parent, Johnson & Johnson, declared they aimed to manufacture 70 percent of "highest volume" products using CM within eight years, increase yield by reducing waste 33 percent, and reduce manufacturing and testing cycle times by 80 percent. Janssen claims the CM methodology it is deploying can reduce operating costs by as much as 50 percent and provide increased production volume while requiring less API and reducing waste. To institute CM processing at the site, Janssen said it collaborated with Rutgers University Engineering Research Center for Structured Organic Particulate Systems (C-SOPS, a leading academic proponent of CM) and the University of Puerto Rico.

Prezista's ingredients must be staged properly and measured accurately. Weighing operations (shown here) are especially critical for proper formulation.

For Janssen, the decision to introduce CM into its operations was neither undertaken lightly nor made over night. According to Mauricio Futran, VP of Advanced Technology for Janssen Manufacturing & Technical Operations, the relationship with Rutgers began nearly 10 years ago. Futran says the strategy to go CM has its roots in Janssen's commitment to enhanced reliability and advanced understanding pharmaceutical processes. It's also part of the reason Janssen joined the Rutgers' consortium as one of its first members. "We share this commitment to enhance the technology we use for manufacturing," says Futran, noting that the CM strategy evolved gradually from that philosophy, and about five years ago the initiative to develop a continuous manufacturing approach rose to become a top priority for the group. "We watched the technology develop and when it really got to where we felt it offered an opportunity to support an appropriate proof of concept, we decided to pursue it and learn how to bring it online."

To many academics, technocrats and corporate proponents of CM like Pfizer, the economics and efficiencies of the methodology are well established. So why aren't Pharma's manufacturers moving to embrace the methodology and develop CM manufacturing facilities in a more wholesale fashion? The simple answer is: it's complicated. Some argue that no matter how efficient CM drug processing is and how large the operational benefits are, the process is never going to beat the "real politic" of the industry in terms of overall operating economics, which explains that the lifecycle cost benefits of CM will never supersede the operating



economics of validated, written-off, large-scale legacy capacity. Scale is another issue some say, and critics complain CM is not cost effective on a smaller or medium scale. Is this the case? "Well, I think the answer really depends," says Futran. "We have done a fair amount of work and we're still doing work on understanding the various factors that impact the financial side of the equation."

For instance, Futran explains the efficiency part of the equation can be impacted by a plant's scale because the cleaning effort and similar will remain relatively the same whether it's a bigger plant or a smaller one. Similarly, the physical attributes the tablet can effect the efficiency "return" of CM methods. According to Futran, his organization is all about "the efficiency," explaining that the 11 elements of efficiency outlined in the company's infographic (next page) form the core list of assessment points that will help Janssen understand the economics and financial performance of CM-based oral solid dose processing within the context of the organization's overall capacity.

BEST FOR SOLID DOSE

Futran says Janssen chose to configure the CM line for the direct compression of Prezista 600 mg tablets because "as you know, it is the simplest way to make a tablet, and we based it on a similar line that Rutgers developed and installed." Explaining that the compound has reasonable drug loading and is very well characterized, Futran noted, "The back [end] process is very stable, so we thought it was an ideal platform to learn how to do this."

Approved in 2006, Prezista (darunavir) is a protease inhibitor (PI) and one of the rare, orally administered solid dose-form biologics. Darunavir is an antiviral medication that prevents human immunodeficiency virus (HIV) cells from multiplying in the body. Wikipedia informs us Darunavir is a second-generation PI designed specifically to overcome problems with the older agents in this class, such as indinavir. Early PIs, says the source, often have severe side effects and drug toxicities, require a high therapeutic dose, are expensive to manufacture and show a "disturbing susceptibility to drug-resistant mutations."

Futran explained that Janssen decided to take the concept to a higher, more commercially acceptible level, engineering the

CM line to be versatile and more reliable. To prepare the line for commercial-ready industrial scale production, Futran says the company's engineers specified more sophisticated controls and enhanced environmental health and safety features.

For example, process analytical technologies (PAT) can play a key role in understanding the process and the elements that work to sustain product quality over the length of a production run. Blend uniformity is one such parameter. "We're looking at blend uniformity and continuity uniformity and ID," says Futran, "to make sure they're all supposed to be [correct] on a real-time basis." But under DOE rigor, the role of PAT technologies has its limits, and do not necessarily offer a means of controlling line stability or process variability. Good process design comes from many places, including experience: "We've learned through a fair amount of work and engineering to run a very stable line," says Futran, "but we really want to get better; rather than stick to a traditional view [of drug manufacturing] and really never get better."

When you have a continuous tablet processing in a commercial setting, raw material intake and preparing excipients, API, etc., is an important operational aspect of CM worth getting right — right from the start. Initial CM operations involve mixing and blending the formulation and staging ingredients and raw materials so they are ready and with adequate supply for a proscribed production run. "There's a room adjacent to the equipment room," says Futran, "where an operator stages various excipients and API. Pneumatic conveyors transport the materials from there to sieves to remove any large materials or faults before they get to volume entry feeders and biometric feeders."

Janssen piloted the CM concept with Rutgers in their facilities, and then using that experience, translated it to a commercial operation. But Futran explains the journey to commercially ready, prime-time production was not exactly a Sunday walk in the park. "It wasn't just copy and paste," says Futran. "There's been a lot of learning: as you do longer runs, as you validate the PAT and the chemometric models, as you learn how feeders are effected by vibrations [and other aspects of operation] like that." Futran says there's always a lot to learn, noting confidently, "So when you learn all those things, you learn how to make a rock stable line." Ultimately, says Futran, he and his team are aiming for real-time release of the product and closer control in the future.

Like any leap into new manufacturing paradigms, getting the financial powers to allocate the company's resources to make the jump can be daunting — no matter how great the projected outcomes may be. Senior management can be very skeptical and reluctant to change, especially when it requires significant investment.

Several operations are necessary to get Prezista from mixing and blending to final tablet form. Tablet press and dedusting operations shown here.

How on board was Janssen's leadership? Futran said the initiative's acceptance and eventual green light had much to do with Janssen's prevailing corporate culture. "I think our senior management is very supportive of innovation, and so the first thing they supported was the membership and participation of the engineering and research center at Rutgers." Futran characterized the attitude of his leadership this way: "I think they strike a great balance of between being very supportive and prudent; prudent and driven. So that's why we had to see what we considered proof of concept at Rutgers before bringing [it to the organization] and then getting an appropriate concept to be built here."

Ultimately, touts Janssen's infographic, the company is looking toward institutionalizing CM methodology throughout its operations, and Futran and his team are ready for it. "We've learned how to set up and control a [CM] line," notes Futran. "We've learned a lot about the business case, all the aspects of its financial liability, environmental impact; all those things."

According to Futran and Janssen, they are assigning priority as to which compounds to develop next for CM processing. "We have an agreement with Rutgers, says Futran, "to begin working with them in partnership [in an effort] to bring a mutual characterization of the products and materials." Judging from announcements describing their commitment to CM, it's clear Janssen has embraced CM as its centerpiece strategy and the future of its manufacturing operations. Is CM the future? When asked, Futran confirms it: "Yes, [Janssen] would like a clear majority of solid dosage forms to be made by these technologies."

DASSAULT SYSTEMES | The 3DEXPERIENCE Company

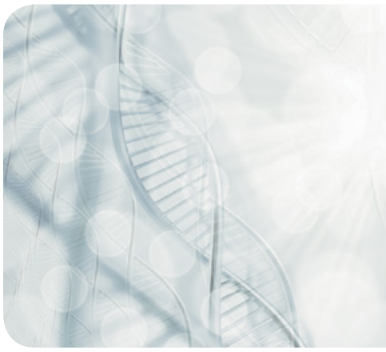
Dassault Systèmes
175 Wyman Street
Waltham, Massachusetts
02451-1223

BIOVIA Corporate Americas
BIOVIA 5005 Wateridge Vista Drive,
San Diego, CA 92121

Telephone: 858-799-5000
BIOVIA.Marketing@3ds.com

HELPING TO BUILD BETTER BIOLOGICS, FASTER

The BIOVIA Biologics Solution is a suite of capabilities supported by a common platform, designed to help with the discovery and optimization of biotherapeutic candidates as well as the optimization of the overall workflow, including the development, manufacturing and compliance processes. It supports the documentation of experiments and the management and analysis of all scientific and quality data generated throughout the process.



Watch this Biologics Manufacturing on demand webinar to learn more at: www.BIOVIA-Biologics.com/Manufacturing

BENEFITS

The BIOVIA Biologics Solution helps to overcome innovation and process efficiency barriers and to minimize compliance risks by providing tools to:

- Process, manage and understand high volume antibody sequence data
- Analyze sequence annotation and activity data together
- Assess developability early in the process
- Easily access and share data
- Rapidly customize and support workflows
- Support, automate and document lab processes
- Manage lab resources, samples and tasks
- Overview bioprocess and quality performance
- Ensure and proof product quality and safety

WHO BENEFITS?

Leaders in Research and Development will see higher quality biologic candidates moving faster towards manufacturing

Leaders in Manufacturing, Quality and Regulatory will see improvements in efficiency and quality and reductions in compliance risk from maximizing and leveraging process knowledge and traceability

Information Technology departments will see decreasing costs by minimizing the number of disparate applications, reducing implementation time and reducing maintenance and upgrade resources

Teams in biologic research, development and manufacturing will have added insight throughout the process allowing the benefit of live data sharing and more informed collaborative decision making for faster and better biologics innovation.

KEY CAPABILITIES:

Discovery and Analysis - Unified informatics tools to simplify the analysis of biology data

Predictive Analytics – Integrated 3D Protein Engineering and Biologics Design for discovery from project conception to lead optimization

Bioinformatics Workflow Support - Graphical scientific workflow authoring support with a large library of components to easily build science processes

Registration and Sample Management - Building and managing consistent, searchable and shareable corporate compound registries

Bioprocess - Streamlining capture, analysis and reporting of scientific information, registration and screening to enhance collaboration, accelerate decisions and improve the efficiency of bioprocesses

Documentation and Data Management - Documenting and managing the flow of information, tasks and materials within and between labs and disciplines

Process Production Operations - Biologics process and quality data access, aggregation, contextualization, analysis and reporting enabling the design of robust GMP processes, visibility into process performance, quality and compliance risk, and improved understanding and control of process and product variability

Regulatory, Quality and Compliance - Controlling data, content and processes for quality assurance and regulatory compliance supporting performance excellence in complex biologics product development environments

VIRTUAL DESIGN & CONSTRUCTION
BRING ALL PARTIES TOGETHERS

A SINGLE-MODEL ENGINEERING PLATFORM TO INTEGRATE THEM ALL

BY ED ROYZMAN AND JOHN GILL, SSOE GROUP

IT IS both exciting and challenging to live through leaps in technology. Current generations have seen the leap from typewriters to word processors, from wired analog telephones to wireless smartphones, from blueprints on a drafting table to Computer Aided Design (CAD) drawings. Today, the building and construction professions are moving from 2D building plans as the standard to 3D building models, or 3D/BIM, which incorporates Building Information Modeling (BIM). In addition to 3D/BIM, technology is now expanding to Virtual Design and Construction (VDC), a complete modern design plan and delivery method, in which 3D/BIM is one of several elements. VDC is exceptional in its ability to integrate the team, the technology, and a total project delivery strategy.

AN OVERVIEW OF VDC

The integration of the design and construction team provides an optimal of collaboration. While 3D/BIM provides its model, VDC uses tagging to encapsulate information about a project across the entire process of design, construction and use of a building. Thus, VDC facilitates collaboration between design, construction and client. VDC is a system wherein the modeling software is a tool, the BIM (model) is the product, and collaborative concurrent engineering and design is the process.

The VDC method has four phases: Plan, Design, Construct and Operate. All four incorporate phase planning (4D) and cost estimation. The planning phase consists of programming and site analysis. The design phase covers a wide range of tasks, including design authoring, drawing generation, 3D coordination, design reviews, analysis of structure, electrical and mechanical needs, sustainability evaluation, code requirements and specification. During the construction phase, BIM is used for site utilization planning, construction system design, 3D coordination, digital fabrication, 3D control and planning, record modeling and material tracking.

During operation, the model helps with building maintenance scheduling, system analysis, asset management, space tracking, disaster planning, and record modeling. At its core, BIM is a database where valuable information can be collected and related to the objects represented virtually in the model. In the hands of a team working collaboratively in the concurrent engineering process, the BIM can be developed and used in many valuable ways.

Designers embed details about each element of each system within the VDC plan. They capture valuable parameters related to every component — whether it is a beam, a wall, a duct, a pipe or a cable tray — all within a finished digital building design. By itself, 3D/BIM certainly helps users make sound, informed decisions, but VDC reaches farther by tagging each piece for construction contractors, fabricators and other trades involved with the project. If a BIM lacks the collaborative element, it is difficult to make the important determinations, and the value of the BIM is diminished. With VDC, designers and others contribute to the model on an ongoing basis, providing enough information to make value determinations about important parameters, capturing valuable information early in the process for later benefit.

Such detail and intricacy can be decisive for designing complex and intensive infrastructure work, such as tight-fitting HVAC ductwork, where it would be impossible on 2D drawings to coordinate and represent every piece of duct work in a tight space. In contrast, BIM reveals space conflicts in virtual reality before any conflict actually shows up. Another win for VDC is faster and more accurate bid pricing because contractors and fabricators can determine down to the individual unit what a structure includes; for example, the number of feet of duct or cable, or the number of ceiling or floor tiles. Similarly, VDC, with its more precise information, reduces on-site mistakes which saves money and time for everyone.

COMPONENTS OF VDC

PLAN	DESIGN	CONSTRUCT	OPERATE
Programming	Design Authoring	Site Utilization Planning	Bldg. Maint. Scheduling
Site Analysis	Drawing Generation	Const. System Design	Building System Analysis
	3D Coordination	3D Coordination	Asset Management
	Design Reviews	Digital Fabrication	Space Mgmt/Tracking
	Structural Analysis	3D Control & Planning	Disaster Planning
	Lighting Analysis	Record Modeling	Record Modeling
	Energy Analysis	Field/Material Tracking	
	Mechanical Analysis		
	Other Eng. Analysis		
	Sustainability Evaluation		
	Code Validation		
	Specifications		
Phase Planning (4D)	Phase Planning (4D)	Phase Planning (4D	Phase Planning (4D
Cost Estimation	Cost Estimation	Cost Estimation	Cost Estimation

The phases of the VDC project delivery process are plan, design, construct and operate. All four phases incorporate phase planning and cost estimation. The process of VDC removes barriers to fully utilizing the informational capabilities of BIM and sharing that model with the construction team and end-user so that the same model can be used again.

A RICH TROVE OF DATA

The integration of the design and construction team allows a holistic view of the project from the standpoint of the owner's business case while ensuring that the input of all the stakeholders is gathered and acted on early in the project. At the outset of a VDC method, a client can provide designers, fabricators and contractors with their own tagging scheme by which to identify both large and small pieces of equipment. Until now, this level of detail would be addressed only after the project is complete, requiring an owner to re-tag items for facility management or regulatory approval (such as FDA approval of pharmaceutical plants).

However, VDC can meet this owner-driven need at the very start of the project, so that value decisions about information parameters can be made before the modeling is complete, eliminating re-tagging time, trouble and cost at the conclusion of the project.

Throughout staging and construction, VDC enables all stakeholders (including fabricators and contractors) to update the building model by detailing and tagging any on-site construction changes for a complete virtual record of a project.

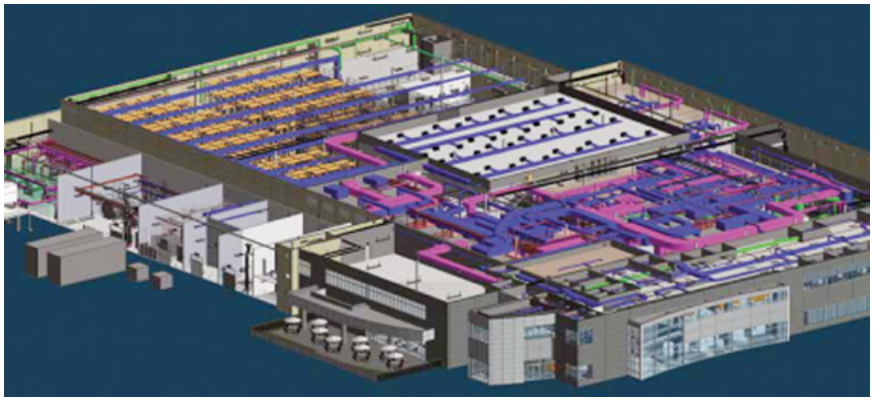
By the end of a VDC method-driven project, designers, fabricators and contractors can input every piece of equipment with number, definition and schedule. A finished project that uses the VDC method has the potential to contain a record of every installed item. Its 3D/BIM component displays the item vertically and horizontally in a 3D model. Building and validation inspectors, as well as facility managers, will all know where to locate every item without a lengthy search. The data in the model can be shared and accessed via a variety of database applications, allowing it to serve as a benchmark for future facility adaptation.

When the finished structure is delivered, its owner and end-users become the beneficiaries, managers and caretakers of a rich collection of BIM data. Throughout the life and operation of the building, users can mine VDC information and add to its depth as the facility is maintained and conditions change. More than just another software package, VDC is a method that fully leverages the capabilities of a single 3D/BIM model through its lifecycle: from design through construction and occupancy/process approvals, all the way through facility use and updating.

Consider a case where VDC is used in a facility that requires FDA approval on minute details such as shut-off valves that must be placed exactly where they were planned and are shown on a model. The owner does not know which valves the FDA will check in the post-construction approval process, so each one must be documented and verifiable. A 3D/BIM model with embedded records is vastly more accessible than 2D drawings for project stakeholders as well as inspectors, and so it is a more efficient delivery and storage method for essential information.

Another setting that demonstrates BIM/VDC's value is in designing and managing industrial production spaces. The model can hold essential information about equipment such as storage bins and down-flow booths, including height, dispersion ingredients and locations, and distance to ceiling

and walls. As the demands of the production process (and of the entire facility) evolve over time, the model's embedded details provide future engineers with the necessary information and 3D images to design transformations from one phase of the facility's functional life to another.



At its core, BIM is one of the elements of VDC, a database where valuable information can be collected and related to the objects represented virtually in the model. More than just another software package, VDC fully leverages the capabilities of a single 3D/BIM model through its lifecycle: from design through construction and occupancy/process approvals, all the way through facility use and updating.

VDC AND VALIDATION

As with data management and modeling described above, integration is also a key VDC contribution to validation. After plant construction is complete, a pharmaceutical company has a year to prove to the FDA that it can manufacture the product in accordance with current good manufacturing (cGMP) practices. Validation protocols, such as filter replacement timing, can be incorporated into the VDC model. So, in addition to the parameters of the objects, the model can be utilized for a maintenance schedule.

In the pharmaceutical industry, validation is the process of establishing documentary evidence that provides a high degree of assurance that a specific process will consistently result in a product meeting its predetermined specifications and quality attributes. Every step, process and change must be properly evaluated before its implementation. Testing a sample of a final product is not considered sufficient evidence that every product within a batch meets the required specification.

Process validation is the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.

Following process validation, installation qualification, operational qualification and performance qualification protocols provide a series of tests and results that support the conclusion that the equipment or systems meet the requirements defined in the Design, Functional and User Requirement Specification. A robust validation protocol contains an explanation of the validation approach and methodology, step-by-step test procedures, and clearly defined, pre-approved acceptance criteria that traces directly to the specification documents, as well as clearly recorded supporting data.

The VDC method brings time-saving benefits to this validation process. The validation technician uses the 3D/BIM model, which has previously identified all cGMP areas with processing equipment, and associated HVAC and utilities to record the checks and verifications for critical components. The owner receives the 3D/BIM model, which has as-built information for the entire facility and process equipment and utilities tagged with information from commissioning and validation efforts.

ELIMINATE THE BACKWARDS STEP

While 3D/BIM models are routinely improving the design process on many projects, the overall VDC method is not yet being used to its fullest extent in most construction projects. For example, many designers use the design benefits of 3D/BIM, but then (sometimes at the client's request) they still output 2D drawings for construction, decreasing efficiency and increasing cost. This backwards step adversely affects both the visible elements, like equipment and furnishings, and the invisible ones, like a building's mechanical and electrical infrastructure. In fact, many contractors and fabricators who recognize the benefits of 3D/BIM create their own models from the issued 2D drawings.

On the other hand, using VDC across a project offers a step forward. It reduces the inherent waste, time, cost and potential for error in 2D drawings, and it generates compressed schedules, a higher quality design, cost savings and an end result that is much more closely aligned with design intent.

The central power of VDC is its integration of the team, the technology, and a total project delivery strategy. The integration of the design and construction team, when combined with a project delivery approach, provides a higher amount of collaboration and allows a holistic view of the project from the standpoint of the owner's business case while ensuring that the input of all the stakeholders is gathered and acted on early in the project.

As the design and construction professions move further into the 21st century, VDC will become the new normal as it enhances BIM. In the fields of design and construction, VDC will prove itself to be the watershed project delivery leap of this age.

FACILITY AND OPERATIONS INVESTMENT

As a result of changing dynamics in the pharmaceutical industry, the availability of used pharmaceutical manufacturing equipment has increased. At the same time, the level of comfort with used equipment has grown. While this trend is good news for pharma companies with surplus equipment, to maximize the potential for investment recovery, it is important that asset owners develop a strategy for managing their recovery efforts.

There are generally three approaches to investment recovery:
1. Complete in-house management using an in-house team dedicated to investment recovery;
2. Outsourcing of all investment recovery services, typically arranged by the purchasing department; and
3. The use of an in-house program manager with support from outside used equipment service providers.

The choice of strategy depends on several factors, including the size of the company, the quantity of used equipment that must be managed, and the resources that are available to support an investment recovery program.

For an in-house program to be successful, the pharmaceutical manufacturer must not only have appropriate storage space (that often must be compliant with Good Manufacturing Practices), personnel, handling inventory and sales management systems, and an advertising budget are required. Outsourcing shifts most of these burdens to the service provider, but someone must take responsibility for overseeing the selection of the provider and for ongoing management of the program at each of the company's locations.

It is also crucial for the investment recovery team – whether in-house or external – to understand the level of return expected by the owner and weigh the other relevant factors important to each individual project, such as the location, project timeframe, and removal costs. If done properly, a customized plan can be developed that maximizes the firm's goals. In addition, experienced teams will not only look for external sales opportunities, but consider internal redeployment as a mechanism for avoiding unnecessary capital expenditures elsewhere in the company.

The purchase of pharmaceutical equipment is in fact a major investment, and access to used assets can benefit both the purchaser, who can save a significant amount, and the seller, who has the ability to recoup some of its original investment.

For pharmaceutical companies with limited experience selling surplus equipment and/or limited resources, used equipment dealers can help facilitate the process. They can not only appraise the equipment, they have established networks of potential customers and extensive marketing programs in place. In addition, they can help ensure that all transactions are transparent and compliant with the various regulatory requirements that govern the sale of use pharmaceutical manufacturing equipment.

Federal Equipment has been a trusted source of pharmaceutical processing equipment for more than 50 years. We are equally comfortable taking on management of the entire investment recovery process, or working closely with in-house management. Our pharmaceutical team has extensive market knowledge, and we consistently exceed clients' expectations with our extensive inventory, climate-controlled, pharma-dedicated storage warehouses, and our ability to complete fast, accurately appraised liquidations.

Matt Hicks, Chief Operating Officer, Federal Equipment Company.

WHEN YOU THINK EQUIPMENT, THINK FEDERAL EQUIPMENT

Federal Equipment Company

WWW.FEDEQUIP.COM

PFIZER'S CONTINUOUS MANUFACTURING POD COMES IN FOR A LANDING

COLLABORATION YIELDS A PRACTICAL, FLEXIBLE, ECONOMICAL VEHICLE FOR SOLID DOSE CAPACITY DEPLOYMENT AND PFIZER WANTS EVERYBODY TO GET ON BOARD

BY STEVEN E. KUEHN, EDITOR IN CHIEF

WHETHER CREATING capacity to ramp up production for a recently approved drug, adding more because a new dose form has skyrocketed demand, or creating a strategy to phase the replacement of aging global capacity, GEA Pharma Systems, G-CON Manufacturing and Pfizer have a new manufacturing vehicle they've been driving, a ride they'd like to share with the industry.

Awarded a 2015 INTERPHEX Exhibitor Award for Best Technology Innovation, the Portable, Continuous, Miniature and Modular (PCMM) is Pfizer's answer to the many issues associated with production capacity —from process efficiency to product quality. Recently the consortium's PCMM prefabricated processing modules were shipped to a building at Pfizer's Groton, Connecticut, R&D facility in a proof-of-concept installation that, by the end of March, was headed for commissioning and validation with operation slated for the end of 2015. In a nutshell, and the "nutshell" analogy fits, the PCMM integrates GEA continuous processing granulization and mixing equipment with smart control systems within a factory-fabricated G-CON POD (portable, self-contained GMP module) to process oral solid dose (OSD) forms.

Although pharma process-line engineering concepts like modularity, continuous manufacturing (CM) or pre-fabricated skid-mounted subsystems are relatively mature ideas, the PCMM integration breaks innovative ground, not so much for the combination of technologies, but in the scale of the continuous manufacturing process it deploys. Phil Nixon, of Pfizer's Pharmaceutical Sciences Technology & Innovation group in Groton, Connecticut, explains that the collaboration was intended to break new ground without breaking any.

"We've taken [the concept] further, he explains, "to make it something that can be readily deployed in a portable manner — we're trying to miniaturize it, make it more modular." Ultimately, says Nixon, who at INTERPHEX 2015 enthusiastically walked *Pharmaceutical Manufacturing* through the "factory," the aim is to achieve adaptability and flexibility. "By itself, continuous manufacturing gives us variable batch size," explains Nixon. "In today's world, a lot of products are [now produced in] smaller volume. We need to be able to change over faster, not only for emerging markets, but to be able to get new technology out there faster with new capabilities."

There's significant value in the concept and Pfizer's Nixon explains that it's going to drive the industry away from its "manufacture-to-forecast mentality," noting that "we have huge inventories that cost a lot a money. With [PCMM] we're going to more of a demand-driven approach. So market demand drives what we make, and therefore inventories will be pushed way down." By using the same exact equipment for development, clinical supplies and commercial supply, says Nixon, a lot less expensive API will be required.

According to Nixon the PCMM concept is a total risk killer, especially when considering the overall equipment and control and automation standardization: "The current way we do batches, you may use the same equipment when you go to a larger scale," says Nixon. "Usually, you're at least scaling up two times, often changing equipment in the process. Then you have different sites involved that [might not know] certain things about the equipment selected to bring things to scale. With the PCMM, it's the exact same equipment from beginning to end."

When a new OSD processing line is likely to take three or more years to design and construct, the PCMM's 12-month design, build, start time frame is a game changer well-suited to meet the pressure being felt by all of Pharma to accelerate their time-to-market performance. Nixon described it this way: "About a month ago, we landed it in Groton at the R&D facility. And literally, in three days, we took these pieces of the POD and the equipment on the four plates and put

Assembly of the megaPOD; top section, left, lifted and bottom section, left, being moved into place (Courtesy of G-CON Manufacturing Inc.)

it all together." Explaining that even with upcoming calibration and qualification, the units would soon be up and running and within about six/seven months: "It's on the ground; it's put together; and we're doing the work to get it up and running for GMP later this year."

According to the collaborators, the PCMM concept was designed to address the rapidly changing requirements of pharmaceutical development and manufacturing, aiming to meet the industry's needs for continuous processing in a flexible, self-contained manufacturing space. Within the POD the process line has three major segments: Raw material dispensing, GEA's Consigma-25 twin screw wet granulization module and a continuous mixing and tablet compression platform. As far as miniaturization, Nixon says a PCMM offers a footprint some 60 to 70 percent less than a comparable "permanent" line.

POWDER TO TABLET IN 20 MINUTES

When GEA Pharma Systems introduced its ConsiGma continuous tableting line, it said the system was "In line with the FDA initiative of quality by design." In fact, GEA presented the system at the FDA's first, Continuous Manufacturing Symposium in 2010 as the only technology supplier ready to present a viable solution.

What has Pfizer and other GEA customers like Janssen Pharmaceutica and AstraZeneca find so appealing is the ability of the ConsiGma line to run as little as 500g in R&D, but also run clinical trial, launch size and any production-size batches. "There is no process scale-up," says GEA, "as time is the only relevant factor in a continuous process. This allows manufacturers to reduce development time dramatically to reduce costs and bring products to market much faster."

PCMM's integration of CM at a seemingly small scale is perhaps counterintuitive to current industry

ConsiGma 25 continuous tableting line is a multipurpose manufacturing platform incorporating blending, wet granulation, drying and (direct) compression, as well as on-line quality monitoring. (Courtesy of GEA)

thinking, which posits that continuous manufacturing of solid dose forms is really only economically viable when it's accomplished at some amazing, giant scale. Nixon reiterates the concept of how scale becomes the subordinate driver of capacity because if one needs to produce more volume, one just runs the line longer to create it. "I chaired the Arden conference in Baltimore. And I think it was fascinating to see that almost every case study was for small-volume applications. I agree, that for decades in other industries, [CM was the choice] for really high-volume products. In this case, we're trying to say [PCMM is] suitable for both small and large volume runs." Nixon says the efficiency of the process is really key, so whether a Pharma company is making a small amount or a large amount, the process is set and validated from the very beginning of development and that the associated cost efficiencies of GEA's package are an affordable alternative that is infinitely scalable by adding more modules.

"We need options," says Nixon. "In this business, the near future is so uncertain. Things change so fast now that you have to have an option to deploy [manufacturing capacity quickly. It'll take us less than a year to deploy [PCMM] versus two or three years for a stick-built facility."

Capable of doing particle design and mimicking any traditional batch granulation process, the granulation, drying and tablet compression lines are designed for "plug flow," which GEA explains is a first-in, first-out process, avoiding back mixing and allowing for control of critical quality attributes in-line.

Maik Jornitz, president of G-CON Manufacturing, said this in the INTERPHEX announcement: "We believe that these small footprint, efficient continuous systems will become the standard in the industry and that brick and mortar batch-based systems will become a thing of the past." While that remains to be seen, the concept has an intrinsic logic and the science is well established.

Richard Steiner, Business Development Manager at GEA Pharma Systems noted that the PCMM Consortium's visionary goals had been achieved through an advanced combination of technology and innovation. "What was introduced and described last year during Interphex 2014 hasn't just been delivered, it's also been proven to work," he said.

Summing it up, Nixon offers the Pfizer vision: "We are trying to get other pharmaceutical companies involved because we want this to be an industry standard. This isn't a proprietary Pfizer thing. We want everybody to use it."

What Is Increasing Generic Drug Costs?

Anti-competitive policies and regulations, waning competition among manufacturers and distributors are to blame, says NCPA

BY DEVON M. HERRICK, NATIONAL CENTER FOR POLICY ANALYSIS

COMPARED TO spending on doctors and hospitals, prescription drug therapy is a bargain. Generic drugs are especially cheap, accounting for 88 percent of prescriptions filled but only 28 percent of expenditures. Within a year after a brand drug faces competition from generics, the average price falls 80 percent or more.

Intense competition usually holds generic drug prices in check. Oddly, during the past few years, many generic drugs that have been on the market for decades have suddenly become more expensive. The price of more than one-fourth of generic drugs rose 10 percent to 100 percent or more in 2014. In other cases, older generic drugs have become scarce and hard to procure. Some of the reasons for drug price increases fall within the supply chain — the path a drug follows from raw ingredients to the consumer.

In theory, generic drugs face unlimited competition, since any qualified drug maker can apply to the FDA to produce a generic version of the drug after its patent expires. The reality, however, is often far different. Due to industry consolidation — and an FDA that is slow to approve new entrants into the field — there are many generic drugs for which there are only two or three competing manufacturers. When only a handful of producers make a given drug, the opportunities for informal collusion increase.

The wholesale drug industry has undergone tremendous market consolidation in the past few decades. Today, three large firms control nearly 90 percent of the distribution of wholesale drugs, resulting in less price competition. Some drugstores also function as small-scale distributors that take advantage of scarcity by diverting drugs in short supply to the wholesale gray market. Most of the drugs used in hospitals must first pass through a GPO. These firms purchase supplies on behalf of numerous hospitals, thereby obtaining lower unit prices on bulk orders. Group purchasers that focus solely on price to the exclusion of having multiple sources of a drug can make the supply chain more fragile.

Many of the drugs rising sharply in price are older therapies approved decades ago. Many manufacturers have dropped them either due to low profitability or in favor of newer generics that are in higher demand. Though it is frequently the case that there are multiple manufacturers of a drug, there may be only one or two suppliers of the raw materials used by all producers. Estimates vary, but about 10 percent of drug shortages are thought to be related to raw material shortages.

Insurers and employers often hire Pharmacy Benefit Managers (PBMs) to administer drug plans and use a variety of techniques to control costs. PBMs encourage enrollees to use cost effective alternatives and negotiate with pharmacies and assemble preferred pharmacy networks to manage drug costs and mitigate the problem of rising prices. When price volatility affects local pharmacies, politicians often attempt to insulate drugstores and local constituents from the pain this causes. In the process, state lawmakers often make the situation worse. The following are some harmful regulations that policymakers should avoid:

- Banning Efficient Pharmacy Networks.
- Restricting Mail-Order Pharmacies.
- Restricting Maximum Allowable.

MARKET CONSOLIDATION, LONG DELAYS AT THE FDA IN PROCESSING APPLICATIONS TEND TO RAISE GENERIC DRUG PRICES.

Generic drugs are inexpensive when there is competition, but less so when conditions on the supply-side of the generic drug market hamper competition. Market consolidation and long delays at the FDA in processing applications for generic drug manufacturers tend to raise generic drug prices for consumers. The FDA currently has a backlog of about 4,000 applications. In 2010 the median approval time for new generic drugs was 27 months. The FDA needs to clear the backlog and allow competition to flourish. This, in turn, will alleviate some of the price hikes caused by market consolidation in both drug manufacturing and distribution. Finally, states need to resist pleas from constituents to pass perverse regulations designed to protect local businesses (and pharmacies) at the expense of competition.

Editor's note: This Executive Summary of NCPA's Policy Report No. 371 has been edited. See the full report here: http://www.ncpa.org/pub/what-is-increasing-the-cost-of-generic-drugs-part-i-the-supply-chain