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Pharmaceutical EQUIPMENT & MANUFACTURING Trends

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By Steven E. Kuehn, Editor in Chief

Tools of the Trade

Pharmaceutical processors are wielding some new tools, nailing down new efficiencies and better drugs in the process

MASLOW WROTE, "I suppose it is tempting, if the only tool you have is a hammer, to treat everything as if it were a nail." For decades, Pharma's been engineering its own "hammer," creating development and production methodologies that tended to treat every potential drug candidate like the proverbial nail. To many, Pharma's hammer became too heavy to wield, not only inefficient at driving Pharma's traditional solid-dose nails but increasingly ineffective at addressing quality issues at the manufacturing level for biopharmaceuticals. Since FDA promulgated Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach, drug makers have invested in its principles slowly if not grudgingly — with some more enthusiastic about it than others, but to a certain extent, it's now generally accepted as the gospel truth. As many should be aware by now, the FDA's first principle leaves little doubt about regulators' intentions: "To encourage the early adoption of new technological advances by the pharmaceutical industry."

Janet Woodcock, director for the Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research offered this at PDA's 2014 Annual Meeting: "The pharmaceutical manufacturing landscape has really changed over the past decade and is continuing to evolve rather quickly," she said. "FDA's regulatory approach is also going to have to evolve to keep up, and some of the most significant changes — including the massive shift from domestic to overseas manufacturing sites, which has affected all of you as well as the FDA — [plus] rising contract manufacturing, the fragmentation of stages of manufacturing, not only by ownership but also by geography and diversification of suppliers."

Woodcock and her regulatory colleagues have also recognized that in spite of its intentions framing Pharmaceutical cGMPs for the 21st Century,

Bioreactor Preferences

FROM AN OUTSOURCING PERSPECTIVE – PART I

DRUG OWNERS AND CMOs BOTH HAVE SKIN IN THE GAME WHEN IT COMES TO SPECIFYING BIOREACTOR TECHNOLOGY

By Kshitij (TJ) Ladage, market research manager, That's Nice

Considering the capacious amount of time and resources an organization invests in bringing a biologic to market, bioreactor selection is one of the crucial manufacturing decisions for an organization. Unlike small molecule, the cost of production plays a vital role in the pricing of biologics. Any cost-saving measures implemented at the manufacturing stage translate to substantial profits. Single-use bioreactors have come a long way since their inception, when single-use was considered revolutionary. Single-use technology has established itself as a popular choice at the preclinical/clinical production stage, and is well on its way to becoming a reliable alternative at the commercial manufacturing stage.

The results from a recently concluded Nice Insight survey quantified the slow induction of single-use bioreactors in the mainstream market. Respondents (biologics outsourcers) were asked about their reactor technology preferences, and there was an almost equal preference for the two types of reactors: stainless-steel and single-use disposable reactors (68% vs. 67%, respectively). There are a few kinks that need to be ironed out, namely the cytotoxicity risks, before single-use reactors can be considered as a standard alternative to the stainless-steel reactors. But given the stringent, methodical and conservative nature of the biopharmaceutical industry, innovative techniques have to pass the rigors of tests, approvals and time before becoming an acceptable standard of operation. The future looks promising for single-use bioreactors; industry analysts have predicted the global single-use bioreactor market to more than double in the next 5 years.

So what exactly does bioreactor preferences mean to outsourcers? Does one select CMOs and realign their bioreactor preferences based on the types of bioreactors offered by the CMO or pick a CMO with equipment that matches their preferences? There are advantages and drawbacks to both options.

Bioreactor selection is a very customized, case-by-case process that is dependent on multiple variables. A CMO may possess state-of-the-art single-use bioreactors, but if the outsourcer requires large 20,000 L stainless-steel reactors to complement a similar setup in-house, the state-of-the-art single-use reactors with 250L capacity will not help the outsourcer. However, a mix of multiple 2000L single-use stirred tank bioreactors along with some traditional SS reactors will give the outsourcer the confidence in CMO's ability to fulfill its goals.

CMO BIOREACTOR PREFERENCE

On the flipside, what is the significance of bioreactor preferences for a CMO? Understanding bioreactor preferences and staying abreast with the industry demands gives the CMO a competitive advantage over other companies the agency's own compliance infrastructure became a barrier to adopting the principles of its own guidance. In response, Woodcock offered PDA's attendees this: "So we're going to set up a team to deal with really advanced manufacturing so that you would have 'go-to' people. If you want to establish some advanced technology you can talk to that team — they would help shepherd it through the regulatory process, including continuous processing, using statistical process control."

Alas, "encouraging" the industry to do something is one thing; actually getting it to do something is another! OK, so folks' heads are in the right place, but in the great continuum of Pharma manufacturing, where is the industry these days when it comes to living the philosophy in day-to-day manufacturing operations?

Recent data does show capital is being carefully invested in "current" process and manufacturing technologies, purchasing that's supporting a slow but continuing retooling to address the market's crazy complexity.

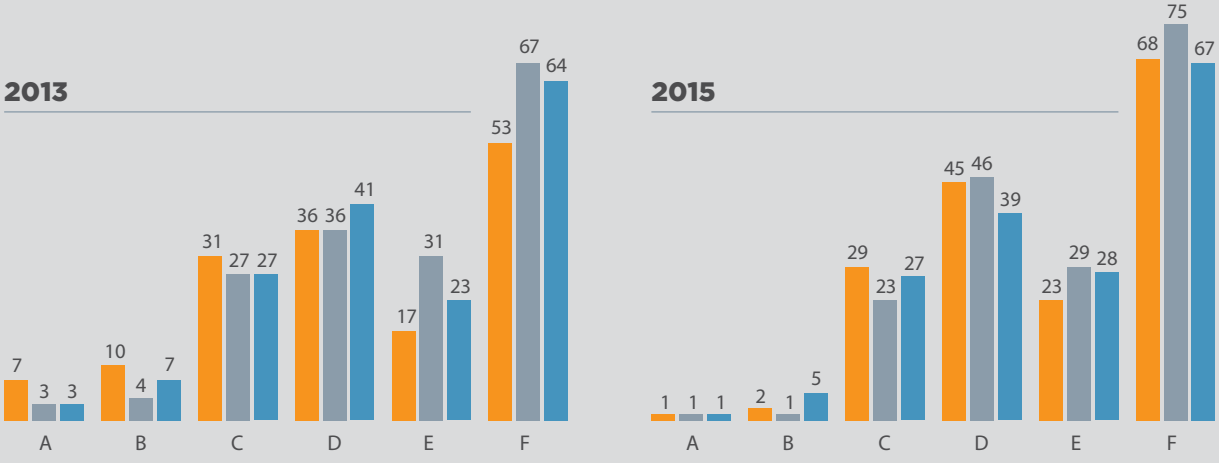
GE Capital's 2014 "Healthcare Industry Economic Outlook Survey" queried 86 middle market healthcare industry service and product firms ranging from $10 million - <$1 billion in sales. According to GE Capital, the majority expect capital spending to remain flat with about 30 percent planning a modest (1 to 5 percent) increase. While GE Capital's findings included companies outside pharmaceutical manufacturing, the results provided a benchmark within the sector. GE Analysts found one of the more "significant" insights to emerge from the study included the opinion that firms are facing margin pressures due to the challenges of growing revenues while coping with the costs of business.

GE Capital highlighted the fact that capital expenditures are likely to focus on replacement of existing equipment, infrastructure maintenance and new equipment purchases. Although recent industry studies reveal a general leveling off with large-cap Pharma moderating capital spending, spending activity from mid-cap firms — like the generic producers, CMOs and the CRDOs — may be ramping up to capture the business

Bioreactor technology preference shifts from 2013 to 2015

Stainless steel technology Flexible stainless steel technology Single-use disposable technology

A. Strongly Avoid B. Avoid C. Indifferent D. Prefer E. Strongly Prefer F. Top 2 Box



vying for business. CMOs need to make sure they have the right setup along with the technical expertise, know-how and personnel to match the reactors. Having the right mix of reactors (stainless steel, flexible, single-use, different capacities) and the right number of reactors will help CMOs win projects/businesses from sponsors.

2013 TO 2015 TRENDS

Year-to-year comparisons revealed that bioreactor preferences have strengthened over the past two years, particularly for single-use disposable technology and the more traditional stainless-steel technology. For the single-use disposable reactors there was a 5 percent point increase in "Strongly Prefer" over the two years whereas the preference for stainless-steel technology showed a 6 percent point increase for "Strongly Prefer" over the same time period.

INDUSTRY TRENDS (PHARMACEUTICAL VS. BIOTECHNOLOGY)

Nice Insight also looked at bioreactor preferences from industry's standpoint. Interestingly, there weren't any significant differences in reactor technology preferences between the traditional pharmaceutical companies and the biotechnology companies. In fact, the preferences were similar except for slight differences in the single-use disposable technology. The Top 2 box preference for stainless-steel technology were 69 percent pharmaceutical vs. 68 percent biotechnology, for flexible stainless-steel technology: 76 percent pharmaceutical vs. 75 percent biotechnology and for single-use disposable technology: 66 percent pharmaceutical vs. 69 percent biotechnology (a slight difference of 3 percent).

Survey Methodology

The Nice Insight Biomanufacturing Survey was deployed to outsourcing-facing pharmaceutical and biotechnology executives involved in biomanufacturing decisions. The 2014-2015 report includes responses from 440 participants. The survey is comprised of 48 questions and collects data on general outsourcing practices and preferences as well as barriers to strategic partnerships among buyers of outsourced services. Additionally, it collects outsourcing preferences on 11 major CMOs servicing the drug development cycle along with performance metrics used to evaluate CMO project performances. For comparison, the results from this study were viewed along with results from a similar study in 2012-2013.

The AIM 8 inspection machine for vials is the first of the new, modular generation of fully automated inspection machines by the Inspection Technology sector of Bosch Packaging Technology.

that's being shed by larger Pharma. GE Healthcare analyst and senior vice president Savant Ahmed added this color to GE's findings: "I think what you're seeing is actually fairly interesting," says Savant. "We are seeing the same trend now spreading to [companies like] Teva and Activis — as well as more of the [biopharmaceutical] pharma side as well."

Savant notes those firms are pretty big in their own right and are carrying some of the same burdens that large-cap Pharma firms used to have exclusive rights to. "With those larger companies, you see CapEx coming down. I think the lag is being picked up by other companies, but it's being done in two ways: One, they're just taking over the capacity that large-cap pharma is getting rid of. So it's not new CapEx. It's basically transfer of assets, so the implications of that are different than if it was like new business."

Nevertheless, there's only so much capacity Pharma can use, but in light of market and competitive pressures, as well as what some might term the "neglect" of the aging pharmaceutical manufacturing fleet, there's only so much idle capacity that's cost-effective to utilize. "Clearly if you look at some capacity, which is very old … it tends to be less on the [solid dose] manufacturing side, but more in the sterile injectable side. A lot of that capacity is old and probably needs to be torn down," says Savant.

It's increasingly clear that Branded Pharma is turning to contract manufacturing organizations (CMOs) to achieve the FDA's vision of the "early adoption of new technological advances by the pharmaceutical industry." Patheon and its parent DPx Holdings are at the forefront of this trend, seeking not only to innovate, but also to lead the industry in integrating and institutionalizing advanced manufacturing solutions and to bring said advancements to their customers.

Bill Weiser, Ph.D., Global Head, PDS Analytical Sciences for Patheon, explains that value for his company's customers is created by delivering speed and productivity. "When you talk about speed there's certainly the efficiency of manufacturing and making sure that we have the right size equipment for the job that we're after," says Weiser, "but it's also speed of development; so in other words, if there's an opportunity for us to accelerate a development program or essentially find the right fit, that creates value for our customers." Speed is one key area, says Weiser, but so is productivity. "For instance, in the solid dose manufacturing area we have made a commitment to continuous manufacturing based on its scalability, process control, and overall operational costs, including footprint." A declaration, which on its face, is interesting because it's a common meme in the industry that continuous manufacturing will only deliver its value when it's applied to the super-high volume, commercial-scale production of (primarily) solid dose forms.

Further, say critics, Pharma is loath to adopt continuous process methodologies (among other things) because in spite of everything, profit margins are so high they can afford the incumbent costs of traditional commercial-scale production methodologies at aging but functional facilities (along with quality excursions and regulatory sanctions) and have no financial incentive to invest in … wait for it … "the early adoption of new technological advances."

Weiser says Patheon is committed to CM for some very good reasons. "One is speed and it's speed both from a development aspect — in other words the ability to go through a number of iterations of formulations design, as well as being able to achieve the right scale for a manufacturing operation." Weiser says this is particularly true during development: "The ability to provide appropriate material for a Phase I or Phase II study, and then be able to very rapidly scale to a larger scale for a Phase III study — essentially just using a continuous train," notes Weiser, "is an opportunity to add value to our customers' programs. So we're involved in that and really beginning to make significant new roads in [CM] technology."

Excellent because the economies associated with CM seem to make very pragmatic business sense, for a drug owner especially if the outfit has a very promising compound that's likely to have decent commercial volumes once it's approved and hits the market. It makes sense then to seek these capabilities and, thinking longer term, understand the potential of a partner that is ready to be with them for at least the first part of that long haul. Weiser agrees, noting "Pharma has really lagged behind other industries in adopting continuous manufacturing. If you think about it, wouldn't it be great to be about to have a process that you could generate sufficient material for a phase two study, and if you rapidly need to go into Phase III that you could accomplish that through basically just running an equipment train longer?" It sure would, Dr. Weiser.

"And if you think about it, scalability is critical for initiating Phase III studies — phase two studies tend to be fairly modest in requirements, but the population for Phase III can be quite substantial — and I think it's those areas where you want to ramp up quickly, or if you have a disease that has a unique therapy solution and a fast-track from regulators, where CM makes a lot of sense." Weiser put it this way: "Get a fast track designation and all of a sudden you've got a good read on Phase II and you're off to the races in Phase III."

EXPANDING THE POSSIBILITIES

Last year, contract manufacturer and packager Pharma Tech Industries announced its intention to expand its Union, Missouri, production facility, adding some 60,000 sq. ft. of manufacturing space for a total of 160,000 sq. ft. The new space, says Pharma Tech Industries, will support production of ingestible powders and will feature a production room built to ISO Class 8/100,000 cleanroom standards. The expansion, scheduled to be completed in March, has all the earmarks of a business strategy supported by enhancing and developing manufacturing operations. PTI recently upgraded its 270,000-sq.-ft. facility in Royston, Georgia, adding an analytical laboratory to broaden its on-site testing for both prescription and over-the-counter drugs. Pharma Tech Industries, says its analytical services, will deploy High Pressure Liquid Chromatography (HPLC) for Assay/Impurity profiles of liquids and powders; Quantitative/Qualitative Fourier Transform Infrared (FTIR) Spectroscopy; Particle Size Analysis of powders by Laser Diffraction; and Gas Chromatography (GC) analysis.

"Our latest expansion and upgrade projects reflect not only an increase in the volume of overall business, but in the variety of manufacturing services that Pharma Tech Industries can offer to customers," explains Tee Noland, chairman of Pharma Tech Industries, in the release. "These projects are in line with our goal of responsible, gradual growth that allows PTI to reach into new areas while continuing to refine and hone existing capabilities." PTI produces more than 300 SKUs of powders and effervescent and solid dose products along with cotton swabs and injection molded components.

What systems or technical platforms does Noland think are delivering great value and competitive advantage to Pharma Tech Industries' customers? "At Pharma Tech we look at technology as a key enabler of our processes and service. For example," he says, "we manage our largest customer relationship via inventory replenishment through an integrated ERP system that communicates directly with our customer's ERP system. We also are looking to digitize more of our quality documentation to reduce related errors and improve customer responsiveness, explains Noland. In addition, he says, nearly all of Pharma Tech Industries' production equipment has systems tied to them in terms of preventative maintenance, shop floor, etc., to help the company maintain and improve production assets.

EXTREMELY SHARP

Besides capacity, Pharma Tech Industries also appears to be intent on applying best practices when it comes to informatics and other information technologies that no one can argue are not extremely sharp tools to help craft operational excellence both from a process and quality systems point of view. "We are really looking to beef up our performance dashboard systems in finance," says Noland, "specifically so we can get the right information to the right people at the right time to help them prioritize what they need to do."

NICE PACKAGING

Friedbert Klefenz has been president of Bosch Packaging Technology since April 2002. Since his tenure began, Klefenz has played a pivotal role in Bosch's ascension to an undeniably strong leadership position in this segment of Pharma processing technology. *Pharmaceutical Manufacturing* caught up with Herr Klefenz at PackExpo to talk about trends in packaging technology and Bosch's role in supporting Pharma's quest for faster, reliable and more versatile systems to handle this increasingly important element of the drug manufacturing value chain. Bosch had a pretty good run, topping $1 billion in sales 2013 and experiencing 20 percent growth from the year prior. Pharma, he said, was a big driver of this business with Klefenz characterizing the company's growth in Pharma as "huge," with more sales to European Pharma firms than he expected, given its sluggish economy.

While Klefenze does not necessarily agree that Pharma's on some CapEx spending spree, he explained that Pharma's spending is dictated by its own particular market environment: "Pharmaceutical companies have a different cycle compared to the economy in the world; one of the pharmaceutical cycles is related to … new product which goes in the pipeline."

Again, it's not about how Pharma is spending, or how much, but what they're spending it on, and Klefenz agrees that Pharma is looking for optimization — everything in the pursuit of quality and risk management — and higher performing, more reliable, better connected systems.

For packaging systems, the framing science has more to do with physics than chemistry, and the systems, especially the high-speed, high-capacity ones, are masterful expressions of industrial automation and electromechanical "magic" that bring new meaning to "state-of-the-art." Bosch had some amazing machines on display, with a dazzling array of well-targeted solutions including its AIM 8 tablet inspector that prepares final dosage forms for their eventual distribution and consumption.

FLEXIBILITY DELIVERED

SCHOTT recently announced it is advancing to full-scale production of its new system for ready-to-use pharmaceutical vials at the company's U.S. facility in Lebanon, Pennsylvania, in preparation for their commercial launch. If one can imagine the hundreds of thousand of vials a parenteral drug maker or CMO filler handles and processes for high-demand sterile injectables, one can also easily imagine that pre-staged, sterilized vials can save manufacturers major time and money.

Prepackaged, sterile, ready-to-fill vials like these from Schott inject efficiencies into parenteral production lines.

Designed in close collaboration with filling-line manufacturers to meet the industry's process requirements, SCHOTT vial system consists of a patented nest that securely holds up to 100 clean and sterile vials in an industry-standard tub. SCHOTT says users can load these directly onto their filling lines without having to perform arduous processing steps, such as washing, drying and sterilizing. Besides simplifying the process, the new nested packaging protects the glass containers from scratches caused by vial-to-vial and vial-to-machine contact. According to Cassidy, "SCHOTT discusses its product ideas with filling line manufacturers such as Bosch Packaging Technology, Bausch+Stroebel, GEA, OPTIMA and VANRX during the development phase."

"Since introducing the adaptiQ concept, we have received strong interest from our customers," said Christopher Cassidy, vice president for the Pharmaceutical Packaging Business Unit at SCHOTT. "Pharmaceutical companies are seeking packaging solutions that enable them to use their existing filling lines in a more flexible way. In order to achieve this, our

vial system is oriented toward the proven tub format used in syringe manufacturing," explains Cassidy. "This means pharmaceutical companies can use the same production line for various types of containers and formats by adjusting only the filling and closing station to the chosen container format. This helps significantly shorten set-up times for changing drug and packaging configurations."

BETTER TOOLS FOR BIOLOGICS

Pharma's headlines are dominated by news from biopharmaceutical companies announcing acquisitions, plant expansions and new drug approvals. What equipment is "trending" in BioPharma? Biologics manufacturers are under the gun because the process is often the product when it comes to the therapies these companies are producing. Among the technologies bringing quality and competitive agility, single-use technologies, analytics and informatics are bringing home the bacon for Biopharma.

Biogen Idec recently won approvals for ELOCTATE and ALPROLIX, its new Hemophilia A and B (respectively) prophylactic infusions. Joydeep Ganguly, vice president of manufacturing and general manager of Biogen Idec's Research Triangle Park, N.C., operations, paints a picture of his facility. "In Biogen's history, the RTP facilities are state-of-the-art and world class." Ganguly notes the phrase "word-class" is very cliché. "But it is world-class, and it's because it was designed in a very thoughtful and very scalable fashion." There have been considerable investments made over the evolution of the facility, says Ganguly. "In 2006, [Biogen Idec] did a huge technology map project [which] upgraded the capacity of the facility," he says. "We are in the process right now of putting a new harvest suite in place." Ganguly says the facility is generally always in a state of positive flux, constantly reinventing itself. "If you take a look at any point in time, I would be comfortable saying that it would rank as one of the more contemporary facilities within the sterile biotic facilities," he says.

Joydeep agreed that incremental advancements in all aspects of bioprocessing — as well as affordable access to technologies (like single-use and analytics) — are bringing the agility, efficiencies and risk management Biogen Idec and its peers are demanding, delivering a new dimension to operations of this scale.

Regarding single-use, "it's not the singular reason why we're getting efficiency," says Ganguly, "it's a combination of facility upgrade, moving to better technologies and moving to high-capacity resins, etc." One of the things that Ganguly says is making a difference is the fact that Biogen is investing heavily in advanced control and advanced-monitoring technologies to drive efficiency because, as he so succinctly put it, "it's very expensive manufacturing."

Ganguly says it's optimal to seek early predictive indicators of the health of your batch before it's actually released. "So the ability to get production done and to see the health of the outcome of your batch can lend itself to an efficiency in terms of your batch losses, or not having predictable measures of success." Waxing enthusiastically about this technology's capability to improve operational excellence, Ganguly notes, "We've made investments in things like cell culture monitoring technology where we have a lot of real-time cell counting methods; we've integrated some really cool ways of applying higher mathematical models where we've actually taken development data and used advanced mathematics to quantify it — the way you scale up."

Ganguly explains that when one scales up, this data is critical. "Scaling from 2 liters to 2,000 liters — which is huge — that is, when scaling from the lab to a large-scale manufacturing facility, modeling is extremely effective in projecting outcomes and managing risk." And then there's an entire space around using big data on the floor, notes Ganguly: "We have so much data at our disposal ... and we make this available to all our business centers." Ganguly says Biogen Idec has a lot of informatics tools "that are on the floor right now where operations start and where we can get a very quick indication of the health of the process and create advanced mathematical models to support scale-up." Ganguly says it was necessary for he and his colleagues to take a leadership role in establishing informatics on the plant floor to get that data. "That's a component weaved into the fabric of our manufacturing operations," says Ganguly; summing things up, "We constantly look for ways where we try and take technologies conventionally thought of as lab equipment and try and see whether or not there's application in our commercial-scale process trains. That is driving a lot of efficiency — not just in our company, but in the overall industry in general."

BETTER HAMMERS, MORE NAILS

For Pharma's tool users, and for its tool makers, game-changing quality and profit boosting innovation is being led by both, but it often comes from very close collaboration at many levels. This was a common theme among the contributors to this story, where the selection of engineering and systems development firms, technology vendors and others created an environment where Pharma's tools could be applied to meet their current and future operational and manufacturing goals.

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PHARMACEUTICAL MANUFACTURING USED-EQUIPMENT TRENDS

OVER THE past decade, many blockbuster drugs lost their patents allowing an influx of generic replacements. This frequently left branded pharmaceutical manufacturers with surplus manufacturing and laboratory equipment. At the same time, manufacturers are being pressured to quickly ramp up their product pipeline with drugs in narrower clinical categories, thus requiring new, more advanced technologies. These two trends created a dilemma for branded drug sponsors, particularly if they had a robust pipeline and needed to remove idled or excess equipment in their manufacturing spaces in order to make space for new products.

Other trends impacting manufacturing included;

- Longer product development and approval times
- Changing product pipelines
- More complex compounds and delivery methods, which did not allow one-size-fits-all manufacturing

A branded drug typically requires customized equipment, dedicated facilities, and redundant capacities to support large-scale manufacturing or packaging for just one product. New products may require completely different manufacturing equipment and packaging lines to support the new processes and demand. When a branded drug has reached the end of its lifecycle, the equipment purchased for that drug may be idled, redeployed, or removed. While the best use for these assets is to redeploy them within the existing facility or manufacturing network, this option is not always available.

At the same time, the branded drug sponsors, CMOs and generic manufacturers all need access to lower costs equipment without sacrificing quality. They resolve these issues by relying on used-equipment dealers that understand the needs of the industry. These special companies have the expertise to resolve equipment equipment dealers can accurately evaluate and appraise equipment, present options for its sale, and provide that equipment to a new owner with up to 80% cost savings over the price of new and with greatly reduced lead time.

Manufacturers are also turning to dealers in emergencies. If a manufacturer has an equipment failure, a dealer may be able to supply equipment to meet an urgent need to restore operations as well as secure back-up equipment to mitigate equipment downtime as a supply risk. Generic manufacturers can secure equipment at lower costs for intense price competition or to take advantage of market opportunities with higher margins. Additionally, CMOs can obtain the equipment they need to win new projects and meet contractual milestones.

Engaging a used-equipment dealer provides the opportunity for significant cost savings as well as the ability to quickly obtain high-quality equipment, and streamline manufacturing.

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VETTER'S CHICAGO OPERATIONS

Start with the End in Mind

Vetter's first U.S. facility brings advanced aseptic filling capabilities and robust risk-management to address critical pre-commercial development complexity

By Steven E. Kuehn, Editor-in-Chief

IN THE pursuit of successful pharmaceutical enterprise, contemporary wisdom suggests that managing the complexities associated with critical preclinical developmental stages may be better left to operational experts outside one's organization. Whatever the underlying business reason for seeking outside support, navigating a promising injectable through trial phases, then seeing it through to commercial-scale production requires intensive operational excellence to accomplish compliantly and successfully. The sky-high trajectory of biopharmaceutical development in the U.S. continues to prompt a steady and growing demand for services supporting injectables development — a promising and lucrative market that five years ago Vetter, headquartered in Germany, knew it could expand to meet, given the right operational footprint in North America.

RIGHT SPACE, RIGHT STRATEGY

In Vetter's capabilities literature, its marketing team characterizes the company as a leader in aseptic contract filling. With more than 35 years successfully providing fill and finish services, formulation support, process development and packaging development services, Vetter's claim of leadership is hard to dispute. The company delivers its service offerings to global customers via three primary business units: Vetter Commercial Manufacturing, Vetter Packaging Solutions and Vetter Development Service (VDS). With so many promising molecules and injectable therapies being developed out there, Vetter's growth strategy began to focus on expanding VDS operations in the U.S.

After a thorough search process, the team — including Claudia Roth, VDS Chicago's president — identified a promising site near Chicago. Roth explains that Vetter considered all of its options in its quest to secure lab and filling process capacity in the U.S., but quickly concluded that finding an established facility with the best combination of location, civic infrastructure, expansion potential and site-specific amenities would create the best basis for Vetter's U.S. VDS operations. Although plenty of idle pharmaceutical capacity may be available, finding the appropriate site for VDS had its challenges, says Roth: "At that time there was not that much wet lab space available." She says that ultimately, the former Searle campus in Skokie, Illinois, offered the best, most flexible site. The campus, now known as the Illinois Science and Technology Park (ISTP) offers tenants, according to ISTP's website, "approximately 2 million square feet of office and state-of-the-art facilities including chemistry and biology labs, GMP and NMR facilities creating a full-service corporate research campus." Vetter's Skokie, Illinois, "neighborhood" is optimal in many respects. For instance, it's a collar suburb of Chicago, has proximity to one of the nation's biggest airports, and the geographically central region supports an ecosystem of Pharma-related businesses along with a skilled and experienced labor pool. "We liked it because of its 'reachability,'" says Roth, noting the logistical benefits stemming from VDS's location. "We can reach Chicago

in a two- or four-hour flight from [the] coasts and we have only a seven-hour time difference from our parent company, so accessibility was good."

Overall, Vetter's facility encompasses about 30,000 square feet with roughly one-third dedicated to manufacturing; one-third to labs and the remaining third devoted to administration offices and warehouse space. "We had the chance to leverage the layout [because it was] a former pilot plant of Searle. But for sure, we had to fully retrofit it," says Roth, "there was not a single piece of equipment that we could use."

One example is the original water for injection generating system Searle installed. Even though it was still functioning it was 30 years old, says Roth, and "did not have the necessary documentation, e.g., material certificates to fully qualify the system to today's GMP standards."

So while the layout and location were optimal, says Roth, all new process equipment had to be installed. "We started in 2010 with the retrofitting of labs and clean rooms. We also installed new utilities and our own water-for-injection generating system." Roth points out that they used the labs to qualify the new water-for-injection facility and get ready to install the clean rooms. "It was always planned from the very beginning that we do a step-wise implementation of clean rooms," says Roth, pointing out that VDS Chicago has a total capacity of three filling lines: the first is a multipurpose line for liquid vials, syringes and cartridges VDS installed and commissioned in 2010. In 2011, a vial line with an adjacent freeze dryer was commissioned; and in spring 2014, Vetter was busy installing its third line for syringes, which primarily enables packaging flexibility and in-line check weighing for high throughput. As of this writing, the third clean room is currently in qualification.

Roth explains that whatever is needed for incoming materials in processing, final product testing, utility testing as well as environmental testing can be accomplished by VDS Chicago labs, including some limited stability testing for customers: "What I mean by 'limited' is that some customers have their own stability chambers, but they do not have all the methods necessary. So they store everything and send us the samples. We perform the analysis and send the results back. If a customer wants to leverage [Vetter's] stability program, we outsource that to our parent company, which has all the ICH conditions and very large stability chambers."

VDS CHICAGO FULLY AUTOMATED FILLER

Clean Room Three contains a fully automated Bosch engineered filler dedicated to fill vials, as much as 10,000 units per batch.

EXCLUSIVELY SINGLE USE

Working with clients to foster their product through early development process is typically challenging because of tight timelines and the often limited amount of material to work with, notes Roth, describing Vetter's early commitment to integrate single-use disposables into filling process operations. "We decided very early on, back in 2009, that we wanted to design the site with the exclusive use of disposables for product contact."

"I think one of the nice things about this site is it draws people in that have varied backgrounds in [the] industry [from] the Chicago area," says Karis Findlan, customer project manager at Vetter's Chicago site. "A lot of us have worked together before or know people that have worked with our colleagues. A lot of people have ties to the site, as well," she says. At her post for two years, Findlan is a Big

Pharma veteran and among the frontline team customers meet to explore how Vetter's experience and operations acumen can support their drug candidate's development and eventual commercial potential. "We have a project management group in Germany that's pretty large," notes Findlan, positioning VDS Chicago operation's within the greater Vetter organization. "It's about 20 people. Their focus is mainly on bringing in products for commercial manufacturing. But there's always been some clinical manufacturing occurring there as well — people want to move into their commercial site earlier, sometimes even during their clinical programs. We have two project managers here at VDS Chicago and our programs are focused on the early clinical phase — preclinical, phase I and phase II mostly. We get involved from the very beginning."

Roth put it into perspective: "We said, 'why start from scratch?' Why don't we utilize all the experience we have. We know exactly what is working in a commercial environment. We decided early on that we want to have a seamless transfer from the clinical to commercial."

Findlan explains that it pays to get involved early, to make sure that what the customer wants is feasible for the site, "which it usually is — I think what is unique about this facility is we have a variety of types of customers. We get the large pharma who have a whole team of people and a lot of expertise … and have all the drug product experience. Some have extensive manufacturing backgrounds. [But] then you also have the very small players who may not have hands-on experience and essential technical know-how. This is their first molecule — they don't necessarily understand supply chain."

Squiring nascent biopharmaceutical therapies from lab to factory is a niche that VDS's Chicago operations are geared to fill, a capability they're eager to leverage for their customers. Findlan explains that certain customers sometimes need a bit of expectation setting when it comes to engaging a CMO/CDMO. "With the smaller start-ups some don't realize how long it takes. They ask 'can I fill next week? I just finished my formulation!' They may not be aware of all the elements that go into drug product manufacturing."

Findlan says from the first time Vetter talks to a potential customer, to the point where they are manufacturing that customer's first GMP batch, the typical duration is about three months and that, on average, projects usually last six months, depending on different parameters.

Of course those are ball-park timelines. Roth and Findlan agree that it really depends on what stage the product is in and how much development work has already been completed. "Some people come to us with a product that they have already produced at another CMO," says Findlan. "They have a process with some data. The first step we always take is to sit down with our process development group and [the customer] and talk about what data they have, what they know about their product, what small-scale studies they've done." That all feeds, say Roth and Findlan, into how Vetter aligns its operations to meet customer needs. "Sometimes

VETTER VDS CHICAGO

DEDICATED TO SMALL-BATCH CLINICAL MANUFACTURING:

- State-of-the-art facility, highly advanced processes
- Provides aseptic filling of syringes, cartridges and vials
- Supports development of preclinical through Phase II products
- Processes designed to mirror those at Vetter's European facilities

FULLY AUTOMATED VIAL FILLING:

- First-of-its-kind Bosch MHI 2020B automated vial filler
- Designed specifically for early-stage, high-value biologics
- RABS & high degree of automation reduce risk of contamination
- Runs flexible range of fill volumes, from 0.3 to 23 ml
- Capacity: up to 10,000 liquid or 6,200 lyophilized vials per batch

SEMI-AUTOMATED FILLING:

- RABS reduces risk of contamination
- Syringes, cartridges and vials
- Flexible unit, easily adaptable to different size packaging formats
- Capacity: up to 500 liquid units per batch

FULLY AUTOMATED SYRINGE FILLING:

- Designed to accommodate ready-to-use primary packaging; pre-sterilized glass and polymer syringe filling

EMPLOYS ADVANCED TECHNOLOGIES TO CUT RISK AND TIME:

- A high-tech combination of walling with built-in gloves and airflow control
- RABS minimizes human contact with products – and risk of contamination

MICROBIOLOGY LAB VDS CHICAGO
Most quality and compliance testing is accomplished on site in VDS Chicago's microbiology lab.

customers don't have a lot of information," says Roth. "So what we tend to do in that case, is talk about ways that we can approach the process [at VDS] and what we would suggest as far as a process flow and other elements. For some products, we recommend a technical batch either with API or non-GMP, or with a surrogate — especially if there's something challenging from a formulation perspective — perhaps the API doesn't go in a solution very easily or it requires a special suspension process."

QUALITY: ALWAYS JOB 1

Roth says there are two main principles guiding manufacturing at VDS Chicago: "Less material and challenging timelines." Economies are important, she said, and one of the primary reasons the facility was designed for the exclusive use of disposables for product contact. "Quality is, for sure, one of our highest, most important goals," says Roth, pointing out that all Vetter's filling lines are located within restricted-access barrier systems which protect the product from operators via rigid walls with steam sterilized and tested insertion gloves. "This is a very high sterility assurance level," says Roth.

Roth explains Vetter also achieves a lot of flexibility with modular systems by featuring and offering clients a variety of different component options. The same flexibility goals, she mentions, apply to primary packaging materials, as well, with Vetter able to work with vials, syringes, cartridges and other complex packaging/delivery solutions.

According to Roth, the facility's newest clean room was deliberately configured for ready-to-use primary packaging. "I think this is a trend," says Roth, more and more companies are starting out with ready-to-use packaging material. "On one hand this is good," she says, "but one has to know and trust those suppliers because you are turning over all sterility-related quality assurance to them."

Regardless of the customer's API formulation or complexity, volume of material, or packaging plans for their product, Vetter's intervention during preclinical to late stage development and beyond continues to prove it can help accelerate a drug's journey to market. With its expanded capabilities in the U.S. now well established, drug sponsors have access to exceptional development and filling services to assist their effort in bringing safe, effective and new therapies to consumers.

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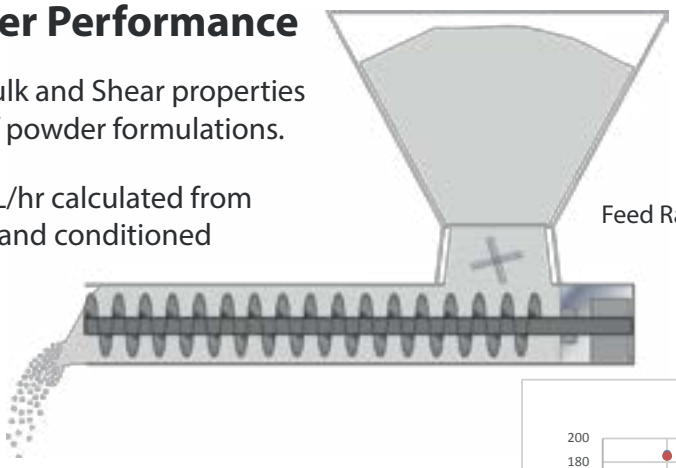
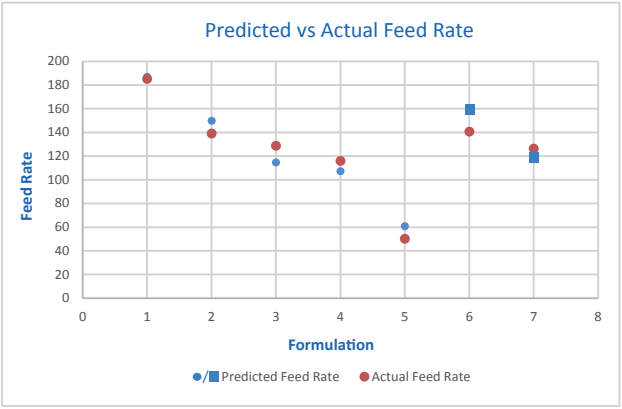


Feed Rate = 49.54 FRI - 13.81 SE + 163.8

$R^2 = 0.9466$

Multiple Linear Regression performed on results (formulations 1-5) to generate relationship between FT4 parameters and Feed Rate.

Relationship validated by estimating Feed Rate for two new blends (formulations 6 & 7) from FT4 parameters, then measuring their actual feed rate in the Feeder.



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PREPARING FOR PHARMA'S

Challenging Opportunities

There's never been a better time to institute safe, high-quality and consistent operations to sustain competitive agility and business success

By Johannes Rauschnabel, Bosch Packaging Technology

NEW LEGISLATION, expiring patents and increasing healthcare costs call for decisive changes in the global pharmaceutical industry. New markets for specialty medicines, biopharmaceuticals and biosimilars are opening up, entailing opportunities for further growth. The coming years will see markets across the globe implement new best practices and manufacturing concepts; what they all have in common is the need for safe, high-quality and consistent operations.

A TRILLION HERE, A TRILLION THERE

According to a recent report by the IMS Institute of Healthcare Informatics, total annual spending on medicines is set to reach the $1 trillion threshold in 2014 and continue to rise to $1.2 trillion in 2017. After a period of turmoil due to patent expiries and austerity measures following the economic crisis, the developed markets are now starting to rebound. The U.S. is forecasted to resume increased spending following implementation of the Affordable Care Act. In Japan, the threat of rapidly increasing medical demands from the aging population urged the government to an unprecedented decision — by 2018, 60 percent of all off-patent prescription drugs are to be dispensed as generics. Overall, lower-cost generic alternatives will continue to have the largest impact on growth. Generic producers and contract manufacturers require very robust and flexible machinery with high output, while complex medicines for targeted treatment demand flexible platforms and smaller batch sizes.

The pharmerging markets will still be extending their progress by 10 to 13 percent, as population increases and rising incomes contribute to dramatically higher use of medicines. Improved access to drugs is supported by economic expansion, significant demographic and epidemiologic changes, and a broad range of government and private healthcare policies. China, the primary growth driver in Asia and beyond to date, now also faces a period of modest decline compared to recent years. This will not only affect local manufacturers, but also pharmaceutical producers from the developed countries who have built a large manufacturing and distribution network in China and have been rewarded with unparalleled revenues. India's healthcare sector, on the other hand, does not seem to stop growing. Pharmaceutical exports from India are forecasted to increase more than twofold over the next four years, if India succeeds in meeting regulatory challenges.

Due to ever-stricter guidelines for aseptic filling operations, manufacturers increasingly rely on the use of isolators.

REQUIRING FLEXIBILITY AND SAFETY

Robust and powerful machines remain the first choice for manufacturing companies in the emerging markets. Especially generic producers want to achieve the highest possible productivity at lowest possible costs. Many drug manufacturers have shifted their focus to the development of new drug formulations and have outsourced their end production such as filling and closing operations and secondary packaging to contract manufacturers. Their main concerns are flexibility and productivity — primary and secondary packaging machines must be adaptable to different products, packaging formats and speeds at consistently high output rates.

Although large-scale production of blockbuster products and generics is still the most prominent manufacturing assignment of the emerging markets, some countries like India also observe a shift to more complex formulations, which has led to a higher demand for sophisticated technologies. The trend towards small amounts of targeted drugs, particularly for the treatment of cancer, calls for flexible platforms that can handle small batches while ensuring the highest safety for both operators and products. Biopharmaceuticals, vaccines and anti-virals must be manufactured and packaged with the utmost caution and attention to detail.

BIOPHARMA'S PATENT CLIFF LOOMING

Having left the largest part of the generic patent cliff behind, the pharmaceutical industry now faces a new challenge. The patents of several large, biotech molecules are about to expire, opening the doors for biosimilar production. In 2002, biologics represented 11 percent of total drug sales; now IMS estimates biologic agents will continue to outpace overall pharma spending and will represent close to 20 percent of the total market value by 2017. Monoclonal antibodies and human insulin will further spur this growth. Biosimilars account for less than 0.5 percent of biologic spending in mature markets; in emerging markets, non-original biologics represent more than 10 percent of all biologics spending, and counting.

Biopharmaceuticals and their successors all require intensive research and development, as well

as sophisticated equipment and contamination-free raw materials, such as Purified and Highly Purified Water and Water for Injection, generated by sophisticated high purity media systems. To deliver the best possible product to patients, drug manufacturers count on safe processing and packaging solutions, while patients rely on their preferred drug delivery devices for safe administration.

As far as these devices are concerned, the pharmaceutical industry has successfully focused its development activities on even safer and easier administration. Although oral dosage forms are more convenient, parenteral administration has taken its place as the most effective and safe treatment. For many biological products there is yet no alternative to parenteral administration. The development of new drug delivery devices increasingly focuses on patients' individual needs. Insulin pens, for example, have been optimized with respect to convenience and ease of use, while the devices generally tend to be smaller and safer to handle.

This capsule filling machine completely isolates researchers and manufacturers from active substances during operation, maintenance and cleaning.

ISOLATING THE PRODUCT FROM THE OPERATOR

The use of high-potency pharmaceuticals has grown extensively, causing manufacturers to pay more heed to protecting all elements of the supply chain from their potentially harmful effects. Protecting products from contact with operators and vice versa has steadily moved up the agenda. Recent equipment solutions favor the use of automation and robotics technology to reduce human contact with the product. Due to ever-stricter guidelines for aseptic filling operations, manufacturers increasingly rely on the use of isolators. Compared to conventional cleanroom production, isolators offer higher product quality, lower operating costs and significant energy savings, as well as a safe accomplishment of longer production cycles.

The U.S. Food and Drug Administration's (FDA) 2004 aseptic guidance states that an isolator "offers tangible advantages over traditional aseptic processing, including fewer opportunities for microbial contamination during processing." The worldwide increase in filling line isolators will continue over the coming years. Vials remain the predominant containers handled in isolators, while the use of pre-filled syringes is rapidly growing, especially in Europe. The development of ready-to-fill sterile primary packaging systems, in cooperation with leading equipment manufacturers, has improved aseptic filling operations and paved the way for the development of new, highly flexible filling and closing machines designed to handle pre-sterilized nested syringes, vials and cartridges.

CONTINUOUSLY CONTAINING HIGHLY POTENT SUBSTANCES

In parallel to the aseptic filling of liquid pharmaceuticals, manufacturers of solid dosage forms have also recognized the need for containment solutions. They prevent biological agents from escaping either into the working surroundings or the exter-

nal environment, thus protecting operators from potent pharmaceutical compounds. Containment systems require closed containers or biological cabinets, and the use of rooms with specially designed air handling and secure operating procedures. Some drug manufacturers have already built entire containment facilities, where building and equipment are optimally fine-tuned to one another. Involving the equipment supplier at an early planning stage ensures flexible, modular and space-saving solutions.

A concept that greatly benefits this approach is continuous processing. Adopted many years ago by other industries like food and chemicals, the pharmaceutical industry only recently started to apprehend the benefits in terms of cost, time, space and material savings. As opposed to batch manufacturing, continuous processing implies manufacturing and processing materials without interruption. This concept will only work if it is based on a thorough understanding of the process interaction between the different unit operations. As Dr. Janet Woodcock, Director of CDER (Center for Drug Evaluation and Research) at FDA, pointed out at the AAPS annual meeting in 2011, "Right now, manufacturing experts from the 1950s would easily recognize the pharmaceutical manufacturing processes of today." Yet the climate has changed in recent years, and leading manufacturers are developing new technologies that focus on reduced costs and improved efficiency.

BUILDING QUALITY INTO PRODUCTS

The FDA strongly advocates continuous processing and has pointed out frequently that the approach is consistent with the agency's Quality by Design (QbD) efforts. QbD is "a science- and risk-based approach to pharmaceutical development and manufacturing […] to help ensure product quality." It aims at defining the quality and efficiency of a product before it is manufactured. Based on these requirements, product quality can be measured and controlled at different stages during the manufacturing process, while taking into account the impact of product and process properties on the final product. With a comprehensive control strategy for material, process and end product, QbD leads to reduced product loss, less production fluctuations and faster time-to-market. The QbD concept is also starting to be applied to biological products such as vaccines. However, the approach for solid formulations

Serialization – ensuring pharmaceutical safety right to the end of the supply chain.

This modular Carton Printing System (CPS) combines serialization, traceability and authentication integrated into a single self-contained system.

cannot simply be transferred to biological products. It still requires more experience and examples to establish suitable review and inspection paradigms.

Process Analytical Technology (PAT), "a system for designing, analyzing and controlling manufacturing through timely measurement of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality," is considered an integral part of QbD. When the FDA issued its PAT guidance in 2004, it triggered the development of entirely new technologies for the in-line elimination of variable product quality. Novel inspection devices, for instance for capsules, simultaneously inspect all quality features like weight, foreign particles and length in real-time and at high throughput rates. On-line checkweighers ensure in-process weight control and deliver exact weights to the filling system for adjustment of fill parameters. Software development and new imaging capabilities further contribute to a rapid advance of these technologies.

SERIALIZING, AGGREGATING, AUTHENTICATING

Once all products have been safely manufactured, filled and inspected, they require one further step before they are brought on the market. Secondary packaging and end-of-line equipment plays a major role in ensuring pharmaceutical safety. Growing Internet sales volumes, production outsourcing and more complex supply chains unfortunately provide numerous opportunities for counterfeit pharmaceuticals to enter the market. Many countries are currently developing and implementing new guidance and legislation to secure pharmaceutical products along the supply chain; for instance, China, Argentina and Brazil, whose health surveillance agency ANVISA adopted a new resolution in December 2013.

The "Drug Quality and Security Act" qualifies the FDA to implement a standard numerical identification (SNI) code for the packaging of all prescription drugs in a step-by-step approach beginning in 2015. The Turkish Pharmaceutical Track & Trace System (ITS) even mandates the serialization of all OTC (over-the-counter) and prescription drugs on a unit level from production to patient. The European Union's Directive 2011/62/EU (Falsified Medicines Directive) also stipulates the implementation of uniquely coded, serialized packs for almost all prescription drugs. At the same time, the EU demands a second layer of security — tamper-proof closures. They clearly indicate whether a package has been previously opened or tampered with.

Pharmaceutical manufacturers are facing enormous challenges to implement the respective regulations within the given timeframe. They must establish new procedures for the management and storage of serial numbers, which in turn requires the adaptation of highly sophisticated packaging processes in-line with global strategies. This calls for a sophisticated software architecture, which is able to integrate the serial numbers consistently on all levels — from devices, line processes and line management to production and enterprise control. A multi-layer and modular machine and software concept is obviously the safest option. It must be compatible with existing line concepts, allowing for the development of a complete system that complies with the industry's demand for safe, high-quality and consistent operations.

ABOUT THE AUTHOR

Johannes Rauschnabel, PhD, is chief pharma expert at Bosch Packaging Technology. He is a graduated Chemist from Eberhard-Karls-University Tuebingen and has more than 25 years experience in R&D and 15 years in the pharmaceutical industry as a product manager for Barrier Systems and as director process engineering. Rauschnabel is a frequent speaker at conferences, a lecturer at University of Hohenheim and an author of multiple scientific papers and patents.

DESIGNING, IMPLEMENTING

Single-Use Solutions

Three single-use solutions save time and money, and enable growth

BY ROB JEWETT, PRESIDENT, TERRACON CORP.

AS COMPANIES in the biopharmaceutical industry increasingly look to single-use technology to cut costs and increase manufacturing efficiencies, their operational leadership is equally active seeking proven ideas and solutions that can meet unique needs. Often product engineers and their teams are faced with options that compromise their specific requirements. Following are three single-use stories where engineering teams achieved reliable site-specific solutions designed to meet challenging specifications.

Their operational/engineering teams sought practical, reliable solutions — to scale up to commercial production, to replace stainless-steel tanks that were failing, and to launch a full product line of single-use mixers filling a market void. For each application an off-the-shelf solution was not an option.

START-UP BIOTECH NEEDS SCALABILITY

When biopharmaceutical manufacturers implement single-use technologies, they gain a number of generally well understood advantages not possible with traditional dedicated stainless-steel systems. Cost control and operational efficiency are some of the key ones, of course.

Dip tubes, like these, were added to the tank covers to enable the company to draw samples at critical intervals in the production process.

Companies are now freer to build less expensive, more efficient and sterile production facilities using a single-use systems approach. This is particularly advantageous for small labs or companies that have completed the research and development stage of product development and want to begin commercial production. These enterprises can now launch products and compete in the marketplace without the capital investment that was once required for entry into the industry.

Recently, a Massachusetts-based biotech research and development firm was preparing to bring a new product to market. The company needed to build an affordable production operation that would enable it to start off producing small quantities of its product and then scale as demand increased. The company invited Terracon into the design process to help develop the cost-effective production environment it needed to meet both its short- and long-term business objectives. Involved from the early design phase, Terracon was able to provide insight and ideas that drove the design process and the creation of the final solution.

TOWARDS cGMP COMPLIANT OPERATIONS

As is the case with most biopharmaceutical operations, it was critical that the production facility provide aseptic conditions both for the mixing process, as well as transitions in order to adhere to current good manufacturing practice (cGMP) regulations. Knowing this was a critical requirement, the biopharma company completed a cost-benefit analysis to evaluate pursuing a single-use solution versus establishing a production environment that would include cleaning and validating the equipment. Confirming single use was the desired alternative, as it would be more economical and faster, the teams moved forward on designing the various components for the proposed production environment.

The production facility includes a single-use mixing system comprised of a dozen 20L custom-configured plastic tanks, disposable

mixing bags, enclosed agitation and aseptic withdrawal lines — all of which work to maintain manufacturing purity. During the prototyping phase, Terracon designed multiple versions of the mixing tanks to help finalize the design. Rapid revisions were possible by working with poly materials and that meant system developers could easily incorporate changes during the design cycles.

The final production system includes mixing tanks using low-sheer mixers and reusable covers that provide the necessary sanitary transition, thus protecting the tank's contents from any contamination risks. Dip tubes were added to the covers, as well, enabling the company to draw samples at critical intervals. Each tank also includes a non-shedding seal around a rotating disposable shaft to prevent contaminants from entering the vessels.

In the end, single-use technology decreased the initial investment required to build the facility, while increasing the flexibility of the overall manufacturing environment. The company can now easily and cost-effectively scale-up operations when demand for its product increases by simply incorporating bigger plastic tanks — up to 200L — and adding larger mixing impellers. The agitation system and other components of the plant will remain unchanged. This start-up company was able to quickly go from manual bench-top processing to small-scale automated mixing in single-use vessels for initial commercialization — no small feat.

When the company realized its expensive stainless-steel tanks were unusable for repeated manufacturing, it turned to Terracon for help. The solution: 600L plastic tanks that met the company's specific production requirements and delivered significant savings.

THAT "UH-OH" MOMENT

When a leading global manufacturer of clinical diagnostic equipment went into production with a fleet of 600L stainless-steel process tanks, the company quickly realized that a certain material was creating batch-to-batch contamination. When the company installed stainless-steel vessels, it intended to reuse them, but discovered that the cleaning process was ineffective, thus rendering the vessels unusable for repeated manufacturing.

Given the expense of stainless-steel tanks, discarding the tanks after each use was not feasible operationally. A less expensive alternative had to be found. The solution: custom-configured cone-bottom plastic tanks that met all of the manufacturer's requirements. To design the solution, the Terracon team met with the production team to detail manufacturing requirements in order to design an alternative using 600L plastic tanks and the appropriate fittings and configurations.

As it turns out, in the manufacturing process materials would flow from a feeder to the tank; therefore, system designers needed to configure the top of the tank to mate with the existing equipment. To solve the problem, the team developed an application-specific top collar with a 15-inch opening to allow ingredients to flow in, and mixers to be inserted. The team then welded the collar to the top dome of the tank. It should be noted that all of the connections and fitting transitions comply with the ASME (American Society of Mechanical Engineers) BPE (BioProcessing Equipment)-2009 Standard.

A SPECIFIC SOLUTION ON DEMAND

In addition to integrating with the existing manufacturing process components, a critical requirement of the plastic tank system design was to conform to aseptic manufacturing practices. To ensure elimination of dead leg and to promote complete drainage, the original tank — molded with a 45-degree slope and a small 6- to 7-inch-diameter flat surface at the bottom — was modified to eliminate the flat, and continue the cone slope all the way to the bottom outlet port. The design achieves two important objectives: complete drainage and improved mixing efficiency. The solution also includes a sanitary outlet port that links up to a recirculation and dispensing loop through which the operator withdraws finished product.

The final aspect of the complete plastic tank solution was its portability. To promote mobility and workplace safety, the tanks (weighing about 75 pounds each when empty) were equipped with handles on each side — an easy fix.

What started out as the need to replace stainless-steel tanks that compromised aseptic manufacturing requirements has, over time, turned into both a

manufacturing solution and a solid collaboration that identified and overcame the company's processing challenges beyond what was originally defined, including aseptic transitioning with the feeder and mixers, improved ease of carrying and moving the tanks, and ports to enable in-process sampling while providing smooth-flowing full-drainage vessels as defined in the initial specification. The customer is pleased because the single-use system solved a serious problem in just four weeks, and the solution not only meets its specific manufacturing requirements, but delivered significant savings as well.

MIXING TANK PRODUCT LINE BROUGHT TO MARKET

One of the most expensive aspects of manufacturing operations has traditionally been the cleaning and validation process required by the Food and Drug Administration (FDA). When manufacturers need to change production from one batch to another batch or from one product to another product, everything needs to be completely cleaned and then validated. Moreover, the validation process requires these companies to undertake extensive and time-consuming documentation.

Single-use systems, of course, solve this problem — and when a global pharmaceutical equipment manufacturer identified a market opportunity for large-scale (up to 500L) single-use mixing capabilities, their engineering and system design team engaged Terracon's team to design and deliver a comprehensive solution. Primary components of the single-use system included 3-D mixing bags validated and certified to be clean and sterile and a cylindrical open-top cone bottom (COC) tank.

One of the key challenges both teams faced was how to place the relatively heavy motor in a position to ensure it engages and aligns reliably with the internal mixing elements without tearing the mixing bag. The team solved this issue by developing a sturdy, hinged platform that mounts the motor and swings up and down in a precise fashion to maintain the integrity of the bag.

Another key requirement was to design a way for the operator to easily replace one single-use mixing bag with another without slowing the production process. They solved this problem by designing a hinged door in the tank sidewall to enable users to reach in to install bags. A transparent window in the door allows visual confirmation of mixing activity. A small cut-out at the bottom of the door also enables operators to access product for sampling. In addition, the carrier comprises custom accessories and features including flared legs to prevent tipping and a base with fully locking casters for mobility, security and stability.

The custom tank supports a single-use bag, which is guaranteed to be clean and sterile, decreasing the risk of contamination. In addition, the new mixing system eliminates the downtime and labor cost that was once required for the cleaning and validation process — and provides complete regulatory compliance ensuring 100% reliability and repeatability.

Together, the two companies designed a highly innovative and cost-effective single-use mixing system. Furthermore, the global pharmaceutical equipment manufacturer was able to launch an extensive line of single-use mixing systems that solved significant challenges in the industry. The new solutions enable biomanufacturers to produce small batches of products while controlling their capital budgets because the systems reduce contamination risks, prompt faster and more efficient production, and avoid costly validation steps.

A hinged door in the tank sidewall enables users to easily replace one single-use mixing bag with another without slowing the production process; the window allows for visual inspection of mixing activity.

This open-top cone bottom polyethylene tank was developed by Terracon as part of a large-scale — up to 500-liter capacity — single-use mixing system for the biomanufacturing market.

ABOUT THE AUTHOR

Rob Jewett is the president of Terracon Corp. He has 30 years' experience in water treatment and fluid monitoring, control and containment. Terracon began manufacturing non-metallic fluid-management tanks, vessels and mixers in 1976 as a cost-saving alternative to stainless steel. Since then, the company has established a reputation for solving complex fluid management challenges with creative and cost-effective custom solutions. For more information, visit its website at www.terracon-solutions.com.

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By Tim Freeman, managing director, Freeman Technology

IN PURSUIT OF WET GRANULATION OPTIMIZATION

Dynamic powder testing in process assures tablet CQAs

WET GRANULATION is a process frequently employed during the manufacture of oral solid dosage forms. The objective is to convert the often fine and cohesive active ingredient and excipients, into more uniform, free-flowing granules that are optimized for downstream processing. Granules that possess ideal properties result in efficient process function, including high throughput and tablets of the desired critical quality attributes. However, this means that the granules produced by wet granulation are typically an intermediate, rather than end product, which raises the question of how to control the granulation process to achieve granules that ultimately make good tablets. In the first instance, it is necessary to identify measurable parameters of the wet granules that can be used to quantify differences in granule properties.

Recently, Freeman Technology, a leader in powder characterization techniques and GEA Pharma Systems, a supplier of pharmaceutical processing solutions, conducted a collaborative experimental study in pursuit of wet granulation process optimization. The work employed GEA's ConsiGma 1 continuous high shear wet granulation and drying system in order to manufacture granules, and dynamic powder testing with the FT4 Powder Rheometer from Freeman Technology. The results obtained demonstrate how the properties of finished tablets can be predicted from dynamic measurements of the wet granules. This finding highlights dynamic powder testing as a valuable tool for accelerating the optimization of wet granulation processes, improving process understanding and control, and supporting the development of a continuous manufacturing approach.

WET GRANULATION

Wet granulation is employed to enhance the characteristics of a tableting blend such that the granules possess optimal properties for processing through a tablet press and into tablets with all the desired attributes. The aim is to produce homogeneous granules that enable high throughput on the press and result in tablets that have the target critical quality attributes, namely assay, weight, hardness and disintegration, for example.

During wet granulation, the active ingredient and excipient components of the blend are combined, along with water, to form granules with a homogeneous composition. These agglomerates, or granules, then undergo further processing — drying, milling and lubrication — to produce an optimal feed material for the tablet press. The properties of the feed material can be controlled through manipulation of a number of processing parameters, including those at the granulation step, where water content, powder feed rate and screw speed are likely to be influential. By altering one or more of these variables, granule properties can be adjusted to ensure optimal performance in the tablet press.

However, to produce granules with specific properties, it is necessary to understand how those critical process parameters will have an impact on the properties of the granules. Equally important is to understand the correlation between granule properties and the quality of the finished tablet. The experimental work described below shows how dynamic powder testing can be helpful in meeting these objectives.

PROCESSING PARAMETERS

The Freeman Technology/GEA Pharma Systems study was designed to determine whether or not the dynamic flow properties of granules from a wet granulation process could be correlated with tablet hardness, a common critical quality attribute (CQA) of tablets. Trials were completed using a ConsiGma1, a lab-based version of GEA's ConsiGma 25 continuous, high-shear granulation and drying concept. The system consists of a patented continuous high-shear granulator and dryer capable of running samples from a few hundred grams up to 5kg or more. Research performed on the system allows for very efficient product and process development, with system residence times of less than 30 seconds. Characterization of the wet and dried granules produced using the ConsiGma1 was carried out using an FT4 Powder Rheometer.

In the first stage of the experimental program, trials were undertaken to evaluate the properties of granules produced when the granulation conditions — water content, powder feed rate and granulator screw speed — were varied. Two model powder formulations, based on paracetamol (APAP) and dicalcium phosphate (DCP), were tested. Process parameters were systematically changed and the BFE of the resulting wet granules was measured. Figure 2 illustrates how the BFE of the APAP formulation granules produced at different screw speeds varies as a function of water content.

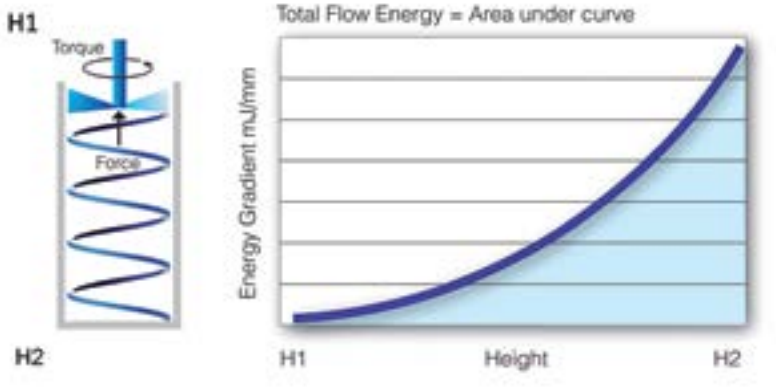

Figure 1: Basic schematic of the FT4 Powder Rheometer operation. Measuring the resistance the blade (or impeller) experiences as it moves through the sample quantifies the bulk flow properties of the granules or powder under test.

	Process Parameters				Granule Properties			
Condition	Screw Speed (rpm)	Powder Feed Rate (kg/hr)	Liquid Feed Rate (g/min)	Moisture (%)	BFE - Wet Mass (mJ)	BFE - Dry Granules (mJ)	BFE -Milled Granules (mJ)	BFE - Lubricated Granules (mJ)
1	450	11.25	15.0	8.0	2217	1623	1283	1526
2	750	20.0	36.7	11.0	2133	1973	1463	1417
3	450	6.0	20.0	20.0	3172	4610	2268	1761
4	750	9.0	30.0	20.0	3342	4140	1951	1795

Table 1: Four different processing conditions used to make two distinct groups of granules.

The data gathered for the APAP formulation show that increasing water content results in a higher BFE if the screw speed is kept constant. Lower screw speeds also produce granules with a higher BFE, for comparable water content. Both trends are to be expected since higher water content and lower screw speeds, which results in higher work input, tend to produce larger, denser, more adhesive granules that present relatively high resistance to blade movement. The data also indicate that at a water content of 11% and screw speed of 600 rpm, the granules produced have a very similar BFE to those generated using a screw speed of 450 rpm and a water content of 8%. This suggests that granules with similar properties can be produced under different operating conditions.

Figure 3 shows how, at a constant water content of 15% and a fixed screw speed of 600 rpm, the BFE of granules produced for the DCP formulation substantially increases as the dry powder feed rate to the granulator is reduced. Additional data show that granules with the same BFE can be made at lower water contents by reducing the feed rate. For example, granules with 15% water content produced at a feed rate of about 18kg/hr have similar properties to granules containing 25% water made at a feed rate of 25kg/hr. As with the studies on the APAP blend, these results show how granules that are identical in terms of a specific powder property can be produced from multiple combinations of processing conditions.

Table 1 shows the different process parameters used to manufacture two pairs of granules with different properties. Conditions 1 and 2 generated BFE values for the wet mass of approximately 2200mJ, while conditions 3 and 4 resulted in BFE values of around 3200mJ. The BFE of the granules was also measured after each of the following process steps. These include drying, milling and lubrication to improve processability, where the flow additive in this study was magnesium stearate. Throughout these stages, the relative BFE values remain consistently grouped, with the BFE values of 3 and 4 consistently higher than 1 and 2.

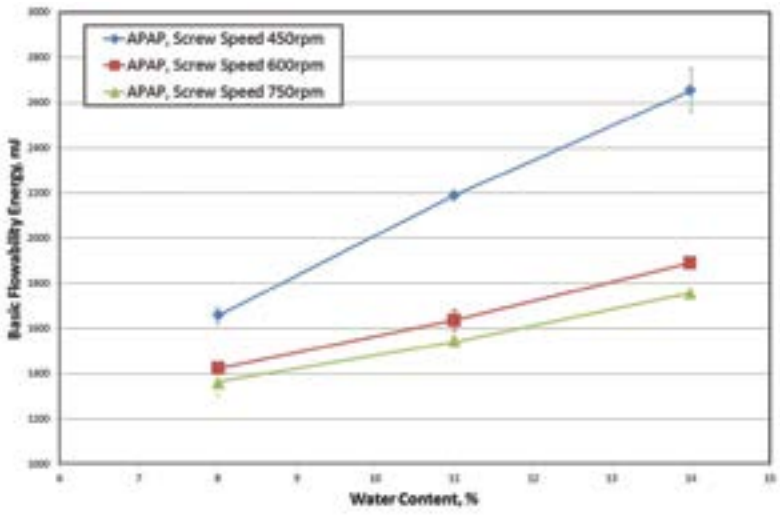

Figure 2: The BFE of granules produced for the APAP formulation increases with increasing water content and decreasing screw speed.

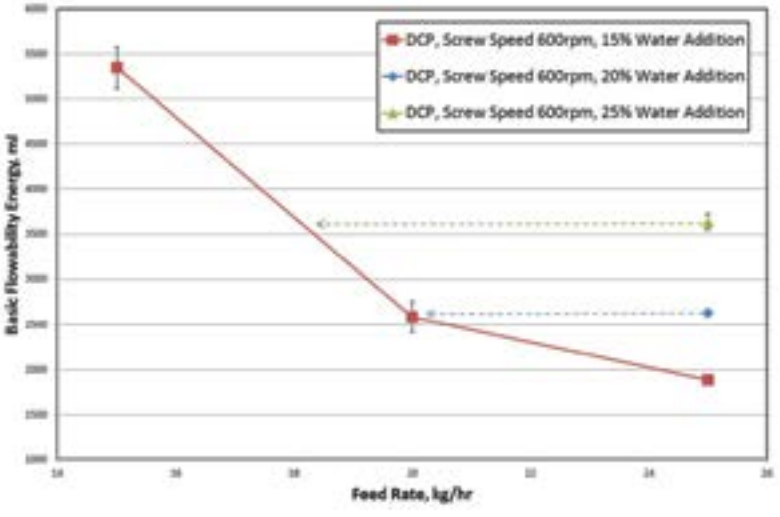

Figure 3: The BFE of granules produced for the DCP formulation increases significantly as the feed rate is reduced.

Figure 4 plots the flow properties of the granules at each stage of the manufacturing process. Conditions 3 and 4 show an increase in BFE following drying, due to the granules' large relative size, higher density and higher mechanical strength, compared to those manufactured under conditions 1 and 2. Following

milling, particle sizes are more similar, although differences in granule density, shape and stiffness still exist and rationalize the observed differences in BFE. These differences are retained following lubrication with noticeable distinctions between conditions 1-2 and 3-4.

These results clearly show that it is possible to produce granules with specific flow properties, as measured by BFE, using a range of different process conditions. Such work demonstrates how BFE values can be employed for product and process development of wet granulation operations. However, they also invite the question as to whether BFE values can be further utilized to predict in-press behavior and, importantly, whether BFE can be related directly to a tablet critical quality attribute?

The four batches of wet granules were subject to drying, milling and lubrication before being run under identical settings on the tablet press. The hardness of the resulting tablets was then measured. Figure 5 shows how tablet hardness correlates with the flow properties of the granules at each stage.

The results show that BFE and tablet hardness are strongly correlated, with particularly good differentiation for the wet mass and dried granules. Correlations for the wet mass and lubricated granules are reasonable, although slightly weaker than those of the dried and milled granules. The poorer differentiation and correlation observed for the lubricated granules is attributed to the overwhelming effect of the magnesium stearate.

This data has shown that there is a direct relationship between the flow properties of the granules at each stage of manufacture — as characterized by BFE — and a critical quality attribute of the final tablet, in this case hardness. This means that once a specific BFE has been linked to optimal tablet hardness, it can be used to drive the optimization of a wet granulation process. These results suggest that, providing the wet granules attain the target BFE, the quality of the end tablet, as measured by hardness will be assured. This offers opportunities to streamline product and process development as well as providing a route to better process control during either batch or continuous granulation.

Today, the traditional batch process approach to manufacturing remains dominant, however, in the coming years many within the industry anticipate that continuous manufacture will be adopted for a substantial share of products.

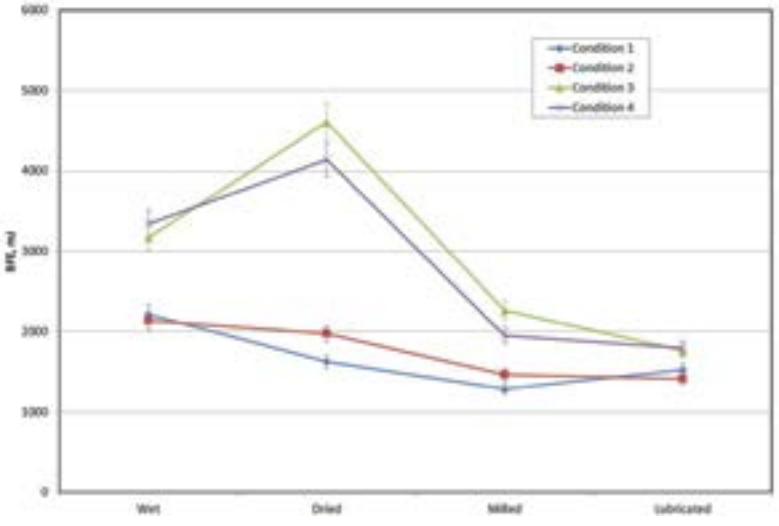

Figure 4: BFE changes significantly during the different stages of granulation, but a distinct difference still exists between granule groups.

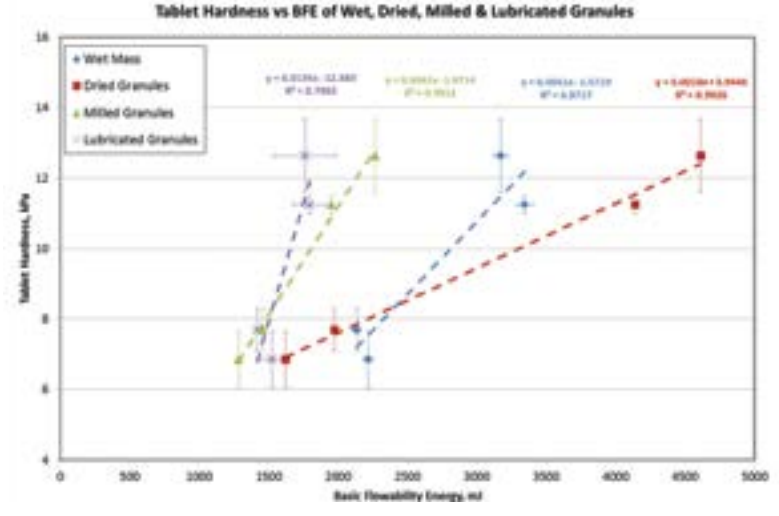

Figure 5: A strong correlation is found between the BFE of the granules and final tablet hardness.

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