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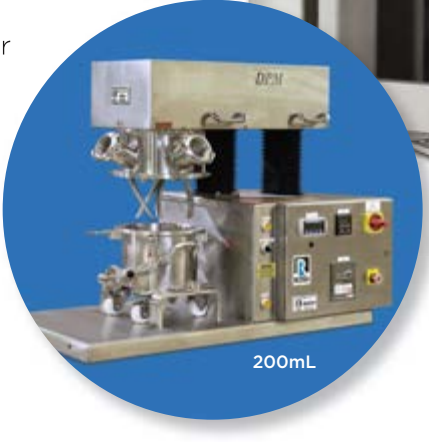
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Karen Langhauser
Chief Content Director

A STATE OF FLEX

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Pharma Manufacturing™ (USPS number 023-188) (ISSN number 1550-6509) is published 10 times a year by Putman Media Inc. (also publishers of Food Processing, Smart Industry, Chemical Processing, Control, Control Design, Plant Services and The Journal), 1501 E. Woodfield Road, Suite 400N, Schaumburg, IL 60173 (Phone: 630-467-1300 Fax: 630-467-1120). Periodicals Postage Paid at Schaumburg, IL and additional mailing Offices. POSTMASTER: Please send change of address to Putman Media, PO Box 1888, Cedar Rapids IA 52406-1888. Phone: 1-800-553-8878 ext 5020. SUBSCRIPTIONS: To receive a complimentary subscription go to www.pharmamanufacturing.com. Subscription rate for non-qualified U.S. subscribers is $68/yr. Single copy rate is $15.00. Other international is $200/yr (airmail only). Canada Post International Publications Mail Product Sales Agreement No. 40028661. Canada Mail Distributor Information: Frontier/BWI, PO Box 1051, Fort Erie, Ontario, Canada L2A 5N8.. Subscriptions/Customer Service: (800) 553-8878

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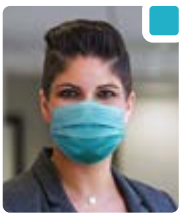
The "it" factory

Do pharma facilities have what it takes?



It's something that everyone wants to have. Those that have it command a presence. They get stuff done. They gracefully adjust, unruffled by life's twists and turns.

Charisma has always struck me as one of those "I'll know it when I see it" kind of things. I don't always know how to precisely define the "it" factor, but I can always spot someone who has it.

For pharma facilities, this factor is flexibility.

A manufacturing plant that can quickly adjust to all the curveballs thrown at it at any given time — change in product, change in demand, change in process? Yes, please.

It sounds desirable — almost magical at times — but once you look past the inherent swagger, what does flexibility actual entail? And could you spot it immediately if you saw it? As I found out while writing this month's cover story, it really depends on who you ask.

When it comes to a universal discussion of the "it" factor, we see it in various forms — actors have it, athletes have it, CEOs have it. In short, it can manifest differently depending on the need and the drivers behind that need. Flexibility in pharma is much the same. If the need is COVID vaccines during a global pandemic, for example, flexibility means speed and scale, and as we've witnessed, manifests as a quick, modular build. But if we are talking about small batch, personalized medicines, flexibility might mean the ability to quickly reconfigure a plant with less downtime in between batches, and then the discussion may shift to single-use facilities.

If you've ever read up on pharma facility design, you're aware that the push for flexible facilities is not a new one for pharma — industry journals certainly don't leave us wanting for articles singing the praises of flexibility. And yet, as pharma has evolved, so have these discussions and so has the concept of flexibility.

And although you might be tired of reading about it, you have to admit that some of the flex-enabling advancements in design, process and technology that have emerged in the past decade are pretty darn cool. You need not look any further than ISPE's Facility of the Year awards if you want to be wowed by state-of-the-art projects. Demonstrating game-changing configurability, portability, scalability and sustainability in different forms, what all these facilities tend to have in common is built-in flexibility.

Unfortunately, "pretty darn cool" can often mean "pretty darn expensive." But as I learned from my discussions with experts in pharma facility design, not all flex is flashy or more importantly, pricey.

In life, many of our examples of people who have "it" happen to be wealthy celebrities, but ultimately, money can't buy charisma. While some people are born with it, most nurture and develop charm — and as with any life skill, the sooner you start, the better. The same goes for pharma facilities. Design decisions (such as making sure ceiling height can accommodate equipment from different vendors) made early don't always add a lot of cost to a construction project and can still pay off down the line in added flexibility benefits.

The flexibility discussion in pharma is ongoing, and like the industry itself, constantly evolving to meet current needs. Like charisma, at first pass, flexibility seems enchanting and a bit mysterious, but as many pharma companies have demonstrated, there are tangible steps that can help get facilities there.

For pharma, flexibility is both practical and attainable — and besides, all the cool facilities are doing it.

industry dose

What we're watching

Highlights from a month packed with informative virtual events

Fixing Broken Medical Supply Chains

A NATIONAL PRESS FOUNDATION BRIEFING

Though this briefing was geared towards journalists, it featured an intriguing discussion from Meredith Broadbent, senior advisor, Center for Strategic and International Studies (CSIS) and a former chair of the U.S. International Trade Commission.

The COVID-19 pandemic exposed serious vulnerabilities in our global medical and pharma supply chains and experts expect that threats to supply chain resiliency will only increase in the future. This newfound attention on supply chain resiliency has created what Broadbent says is a "dangerous momentum" for a U.S. government policy focused entirely on reshoring supply chains.

Broadbent asserted in her presentation — which complements a recent CSIS report — that "no single country can produce all that it needs to fight COVID-19, let alone cure it." Instead, policymakers should opt for an approach that builds resiliency through diversification, trust and communication.

CSIS suggests that Congress should authorize the Office of the U.S. Trade Representative to negotiate a reciprocal "trusted partner network." This series of networks would support international cooperation and help industries respond to new global challenges. According to Broadbent, "experience and economic reality suggest that the path to more resilient and secure medical supply chains is through rational diversification, flexibility, and closer cooperation with trusted partners, not protectionism and government directives to make everything at home."

AIRED MARCH 16, 2021

An archived presentation is available via the National Press Foundation's YouTube channel. The report is available for download on CSIS.org

2021 PDA Annual Meeting

PARENTERAL DRUG ASSOCIATION VIRTUAL EVENT

The Parenteral Drug Association annual meeting is designed to examine the current biopharma manufacturing environment and explore how companies are adapting through the modernization of facilities, approaches and processes. One of the more colorful sessions this year was a presentation from Jeffrey Baker, deputy director, Office of Biotechnology Products, Center for Drug Evaluation and Research, FDA.

Baker opened by applauding the biopharma industry on their progress with COVID-19.

"We are turning the corner because of the work of the biopharma community, doing what needed to be done, when it needed to be done," said Baker.

And yet, Baker challenged whether, overall, we are seeing the same energy and innovation and willingness to get it done in manufacturing that we've seen in discovery and development.

According to Baker, although more than 90 percent of FDA submissions are supplements to Biologics License Applications (BLAs), very few, if any, reflect modernization or deployment of new manufacturing technologies. He says the agency is "not seeing continuous improvement and continuous learning." Instead BLA supplements mostly consist of adjustments of the buffer, label, concentration or site change.

"So what's up with this?" Baker asked. Is it the fault of regulators? He argued "no," pointing out that the FDA has encouraged development of advanced manufacturing technologies for 20 years through strategic plans, working groups, partnerships and programs.

In January 2019, as part of an active listening program, the FDA partnered with the National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) and had discussions with 11 major pharma companies about the adoption of

MARK YOUR CALENDARS!

While some pharma trade shows are slated to be held in person this fall, the current spring/summer lineup has transitioned to virtual. Here's how the schedule looks.

AAM Access Annual Meeting

MAY 26-27 / VIRTUAL
This interactive conference brings together policymakers and influential leaders from across the generics and biosimilars value chain.

BIO Digital

JUNE 10-11 AND 14-18 / VIRTUAL
The Biotechnology Innovation Organization's yearly event has gone digital with a host of high-profile speakers including Dr. Anthony Fauci, director of NIAID, and Julie Gerberding, executive vice president of Merck.

DCAT Week

JULY 12-16 / VIRTUAL
Tune in for educational seminars and discussions about key trends in the bio/pharma manufacturing world.

CPhI North America

AUG. 10-12 / PHILADELPHIA, PA
Industry pros representing all aspects of the pharma supply chain converge to showcase innovative offerings in pharma.

new manufacturing technologies. They asked manufacturers, "With respect to the regulatory landscape what changes would you like to see implemented that would enable your company to deploy innovative technology for manufacturing and continue improvement?"

The key outcome? There is rarely a business case for implementing new manufacturing technologies. According to Baker, this was "interesting in its refreshing bluntness." Companies reported that pre-launch, new technology poses a risk to timelines. And post-launch, global change management, including maintaining separate process for different markets, is a hurdle.

Ultimately, concluded Baker, it should be about optimizing value and not minimizing costs. "Until we look at manufacturing as a value center not as a cost center — something to be optimized rather than minimalized — we are never going to engage the innovation engine that is driving discovery, driving target validation, driving new public health solutions, in manufacturing."

AIRED MARCH 15-17, 2021
This presentation, as well as additional event content, is available on-demand at Eventscribe.net/2021/PDAAnnual.

Pittcon 2021

ANNUAL PITTSBURGH CONFERENCE ON ANALYTICAL CHEMISTRY AND APPLIED SPECTROSCOPY
VIRTUAL EVENT

The annual Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy is a favorite among those looking for the latest innovations and solutions to lab challenges. With the theme "Science: Now more than ever," Pittcon 2021 was an all-virtual event for first time in its 72-year history.

Pittcon's keynote talk, known as the Wallace H. Coulter Lecture, was delivered by Joseph Powell, former director of the American Institute of Chemical Engineers and retired chief scientist from Shell.

When it comes to energy sources, "prepare for change, the future will surprise you," said Powell. With multiple energy sources now available, the focus has shifted to selecting and optimizing the most sustainable options.

"Sustainability is now about addressing climate change and not the lack of access to energy," said Powell.

During his lecture, Powell discussed the historic and current role of industrial labs and chemical industry innovation in delivering on society's needs for a sustainable future. Most developments have been driven by the need to deliver cleaner product to the marketplace, using processes that reduce environmental footprint.

Powell pondered: How do we move wind and solar into the energy system, while continuing to use natural gas in a cleaner way? His lecture presented case studies in technology development that will help manage CO2 and carbon during the energy transition over the next 50 years so that we can meet important climate change goals.

AIRED MARCH 8–12, 2021
Conference sessions are available on-demand until June 12 at Pittcon.org.

Karen Langhauser
Chief Content Director

A STATE OF FLEX

Finding clarity in pharma's quest to attain ultimate flexibility

Among the many darlings of pharma press releases, the descriptions pertaining to the industry's manufacturing facilities are particularly enchanting. "Factory of the future." "State-of-the art." "Cutting-edge." "Next-gen."

All of these descriptors communicate an underlying desire that characterizes so many pharma facility projects: achieving a state of flexibility.

There are currently over 7,000 active pharma/biopharma construction projects happening around the globe. Companies are spending close to $200 billion to build, expand and update their pharma facilities in the race to get their products into the hands of patients as quickly and safely as possible.[1] For decades, the discussion of flexibility has permeated every stage of these pharma facility projects; its praises have been sung by regulators, industry working groups, engineers, solutions providers and of course, pharma marketing teams.

"Everyone talks about getting to that magical place where you can keep the same facility and equipment but just change out the product. This is an admirable goal but it is a long journey taken mostly with baby steps and the occasional hop with a change in technology," says Bill Brydges, reflecting on his 40-year career in engineering and construction.

But once we pull back the curtain, what exactly does this "flexvana"* entail?

* "flexvana" term borrowed with permission from Ken Anthony

Ultimately, a flexible facility is one that is agile enough to adapt to change — whether it be a shift in capacity needs, regulatory demands, manufacturing processes, technologies, products or some combination thereof.

And pharma is no stranger to changing circumstances: An unexpected regulatory rejection, the availability of new or better technology, a crucial piece of equipment that's been backordered, a specific raw material that is suddenly in high demand, or even a global pandemic will test a facility's ability to adapt.

While this sought-after state of flex may seem blissful, anyone in the industry who has been involved with constructing or expanding a pharma facility will tell you the road to get there is anything but. It can be gritty, frustrating, expensive — and paved with uncertainties. And even then, the completed project is still likely to fall slightly short of euphoric flex.

But the good news is that flexibility isn't elusive, and the more pharma can refine the drivers behind their respective flexibility journeys, the more clarity the industry will have in terms of how to get there.

The evolution of flexibility

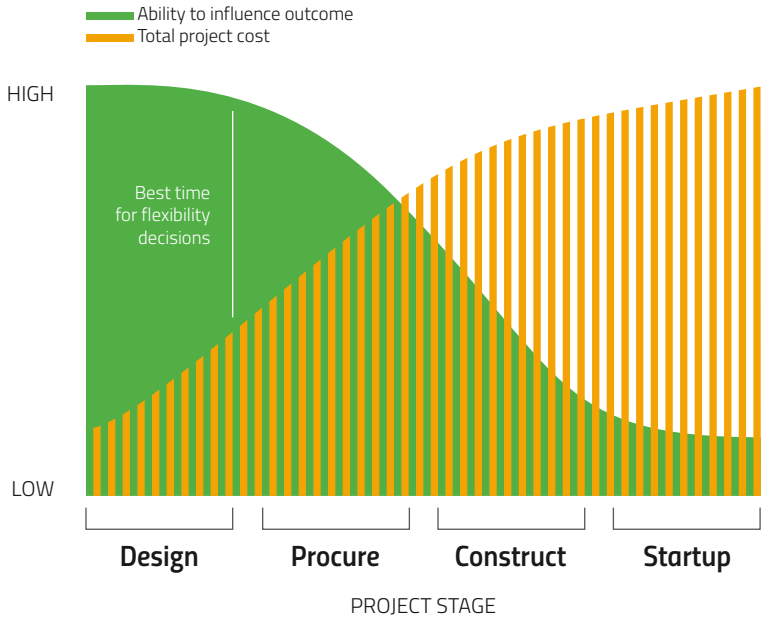
While the pharma industry can be credited with many life-changing discoveries, it did not invent flexibility in manufacturing.

Similar to quality, flexibility in manufacturing emerged as a strategic imperative.[2] In the 1970s, facing increased global competition from world markets and changing consumer demands, American manufacturers began to move away from the Ford method of mass producing standardized goods. By the '80s, consumers were more sophisticated and niche, and manufacturers had to incorporate flexibility into their factories and processes to compete.

In pharma, discussions about flexible facilities, mainly centering around the desire to make multiple products in one facility, started picking up speed in the '90s. Many credit the push to upstart biotechs that — whether out of financial necessity or inherent innovativeness — were looking for more efficient ways to bring new drugs to market.[3]

EXHIBIT 1

Timeliness of decisions



In 2002, the U.S. Food and Drug Administration (FDA) jumped on board when they announced a significant new initiative, Pharmaceutical Current Good Manufacturing Practices for the 21st Century. According to the agency, this document launched the FDA's "vision of a maximally efficient, agile, flexible manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight."

In his comprehensive overview of flex history,[4] Jeffery Odum, vice president of Biopharma Life Sciences at Exyte, points to another significant milestone: In 2004, the International Society for Pharmaceutical Engineering (ISPE) published its Biotech Manufacturing Facilities Baseline Guide and in it, discussed an evolution in facility design. The guide demonstrated that moving from the more traditional open-system, classified space to a more closed-system design could provide enhanced flexibility in manufacturing options. Essentially, manufacturers could choose to contain their individual process steps that were vulnerable to contamination, rather than having to monitor the environment in the entire manufacturing space — this lead to cost savings and scheduling efficiencies.

From there, the concept continued to evolve as manufacturers pushed flexibility boundaries and equipment suppliers stepped up their games, introducing new enabling technologies, such as single-use systems. If processes were safely contained in closed systems, why not manufacture in a large space where you can wheel equipment in and out as needed? Why not run multiples processes in one space? This thinking gave birth to the ballroom concept — a large manufacturing area with no fixed equipment and minimal segregation thanks to the use of closed systems.

At the same time, monoclonal antibodies (mAbs) were becoming the bell of the biopharma ball as the modality's vast therapeutic potential was contributing to its rising popularity. This worked out well, as large-scale mAbs were particularly suited for manufacture using this closed-system, ballroom facility design.

The most famed example of this paradigm in practice is Amgen's Singapore facility, built with a focus on mAb processing. Formally opened in November 2014, the facility had all the flexibility bells and whistles. Using a modular and reconfigurable design, the facility was built in half the time of a conventional plant. Instead of custom equipment that's welded together, the single-use equipment in the plant could be reconfigured, allowing operators to wheel in new equipment as needed. Through the use of technology and process efficiencies, the facility occupied about one-fifth the size of a traditional pharma plant but maintained a comparable level of output, and was able run at one-third of the conventional operating expense.

The plant, rightfully so, won multiple awards and was heralded as the "facility of the future."

But the facility of the future is truly a moving target — and today, that target is starting to look different.

"The facility of the future — those large open ballrooms — were really intended to be for a monoclonal antibody process," says JP Bornholdt, director of SlateXpace Technical Operations at CRB. "But cell and gene therapies have been a complete reawakening in what biotech really is. The industry has yet to determine a coherent vision about what the facility of the future looks like for advanced therapies and what those manufacturers will need — but flexibility is definitely part of that vision."

As history has shown, even as pharma's vision of the future shifts, the industry's quest for flexibility is here to stay.

Flexing in pharma's mirror

One important takeaway from the Amgen model is that in pharma, flexibility comes in many forms. Flexibility can be realized through aspects of facility design, technologies and equipment, and manufacturing processes.

According to Odum, this is one of the biggest stumbling blocks the industry has hit in its quest for flexibility.

"One issue is the definition of flexibility. Is it driven by operational issues, products, other items? It is not always consistent between customers," he says.

Determining what is driving the desire for flexibility is often the best place to start.

Some pharma manufacturers want a facility that can be physically scaled up or down to meet changing demands for products. Some want the ability to move equipment from one suite to another for quick changes in production plans. Some are striving for a multimodal facility that can be adapted to make different types of drugs.

Ken Anthony, who has 30 years of experience in engineering and construction for manufacturing, stresses the importance of having this discussion with clients.

"You really have to dive into what the customer is 'needing and expecting' from flexibility," says Anthony, who is currently vice president of Strategic Development at Binswanger, a commercial real estate and advisory firm.

The conversation is also happening internally for pharma companies.

"It ends up becoming somewhat of a philosophical discussion within the firm. It really depends on the output requirement and the goal of the individual facility," says a director-level facilities manager at a major American pharmaceutical company. "For example, you can use a flexible facility to delay any larger capital spend for a product that may have a lower probability of success. Or, for something such as a gene therapy, flexibility of single-use equipment offers speed in terms of cleaning turnaround and validation."

> **Flexibility comes at a cost which must be justified and included in the project budget.**
>
> —Bill Brydges

When it comes to costs, the timing of these flexibility-based decisions is important. As is the case with project design decisions in general, the earlier the better. The Construction Industry Institute uses a "cost-influence curve" to illustrate that it is much easier to influence a project's outcome during the project planning stage when expenditures are relatively minimal than it is to affect the outcome during operation of the facility when expenditures are more significant. (See Exhibit 1).

Pharma companies and construction firms alike agree that developing a detailed plan of how flexibility is to be delivered upfront is crucial, but Anthony says it's ideal to level-set expectations because even the best-laid plan isn't foolproof.

"The concept of flexibility tends to morph over time. You may agree to what flexible means at the beginning of the project, but while you're building the facility, circumstances change and all of a sudden your flexibility isn't flexible enough," Anthony says. "Because who knows what's going to happen a year

The North American pharma/ biopharma industry is reportedly spending **$52.1 billion** on plant expansions and additions and **$36.8 billion** on new plant construction

— Industrial Info's 2021 Industrial Market Outlook[1]

from now? How do you translate that uncertainty in the flexibility requirements for a facility? There's really both an art and a science to it."

The modular panacea?

A recent CNN article noted that one reason Pfizer was able to rapidly scale up COVID-19 vaccine production to millions of doses was the drugmaker's strategy of using prefabricated, modular construction. Pfizer installed around 13,000 square feet of modular rooms in its Kalamazoo plant that had been pre-built in Texas and then shipped out to Michigan.

But the use of prefabricated modular construction is not a new strategy for Pfizer. In September 2013, Pfizer, along with partners GEA and G-CON Manufacturing, formally launched what the drug-maker called its PCMM concept — Portable, Continuous, Miniature, and Modular development and manufacturing — with the goal of adding more speed and flexibility through the use of prefabricated pharma manufacturing PODs.

The term "modular" — which can be used to describe both a facility's design concept and equipment — commonly enters the flexibility discussion and at times, the two words are even used interchangeably.

Modularity can be achieved in a number of different ways. A modular build can be accomplished by assembling modular panels on-site; or the entire facility can be built module-by-module off-site, tested, taken apart, shipped and reassembled on-site; or, as in the case of Pfizer, facilities can be prefabricated — meaning assembled and tested off-site then shipped whole.

Bornholdt points out that an added bonus of some modular prefabricated units, such as modular cleanrooms, is that they can be considered capital equipment rather than capital improvements, and are thus depreciated at an accelerated rate, resulting in tax savings.

As the pharma industry begins to turn its attention more towards advanced therapy medicinal products (ATMPs), companies are managing highly complex product pipelines and are often unsure which modalities will move successfully through clinical testing, heightening the need for flexible solutions — and many companies are finding this through these modular builds.

"We found that a lot of our ATMPs clients had pipelines consisting of various combinations of gene therapies, cell therapies, autologous or allogeneic stem cells, etc. Especially when it came to contract manufacturers, they almost didn't know what drug they'd be manufacturing next, or what their business needs were going to be," says Bornholdt.

In these scenarios, the fast-paced construction project offered by modular preconstructed suites can allow capital expenditures to be pushed until later in the development cycle.

"If you committed to building a giant stainless steel facility five years ahead of time only to find out that a molecule in development failed, then you have a plant that's at half capacity or less, and it's either way undersized for the next drug or potentially way oversized," says a senior engineer at a major American pharmaceutical company.

This delay in big capital spend minimizes investment risks, allowing companies to make more informed, better-timed decisions.

Yet, while modular is closely aligned with speed, it doesn't always equate to flexibility. Once interconnected, modular facilities can become just as inflexible as traditional facilities. Additionally, Anthony points out that when it comes to prefabricated modules, the units are able to save construction time by using standardized designs. But when pharma companies require more customized designs, it complicates the situation.

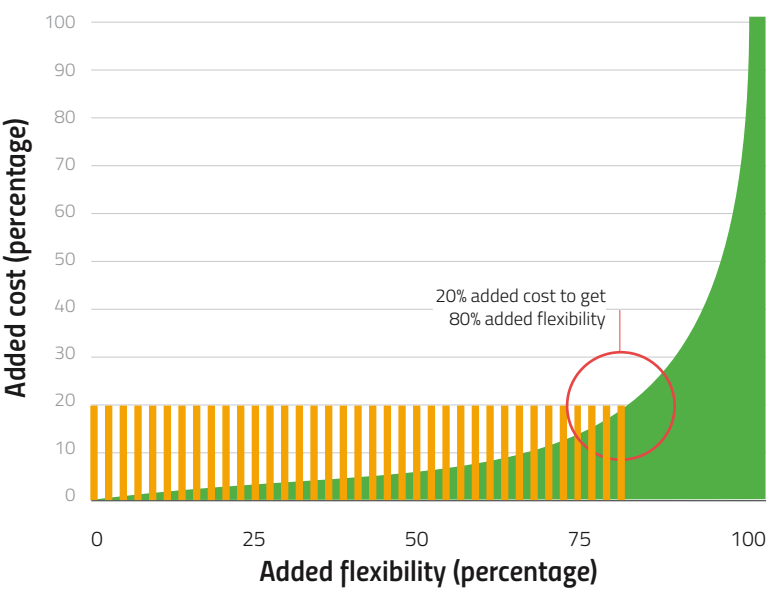
"Modular is not inherently flexible — it was set up for rapid deployment and rapid scale up," says Anthony. "Prefabricated modules are not really set up for you to start cutting into them and monkeying with them. If you go into a modular design and you start doing extensive customization, at some point, it's no longer modular."

Vendors of modular solutions are beginning to address this sticking point by finding the right balance between standardization and customization. The balance was not lost on CRB when the company introduced SlateXpace, a customizable turnkey facility solution based on the principles of flexibility and modularity. According to the company, the problem with offering a single standardized solution is that "when you try to fit everyone, you wind up fitting no one."

"We use modular as a tool to gain advantages of flexibility and speed, but our SlateXpace approach is not limited to modular delivery. Over the course of nearly 350 advanced therapy projects, we've found the best practice is to start with a set of carefully planned design blocks based on function — then arrange those design blocks to form a complete facility layout unique to each client's process and manufacturing goals. That design is realized by blending the best attributes of various construction delivery methods — modular, panelized and stick-built — utilizing each in the appropriate location and ratio to deliver a facility that also meets the client's particular business drivers, such as budget and schedule," says Bornholdt.

EXHIBIT 2

Flexibility vs. cost



Grabbing the flex fruit

It's a classic case of "is the juice worth the squeeze" as pharma manufacturers evaluate the sliding scale between costs and benefits of different levels of flexibility.

"When it comes to building in flexibility, it's certainly not impossible, but you have to keeping asking yourself 'is it worth it?' Flexibility comes at a cost which must be justified and included in the project budget," says Brydges, who now serves as chief executive officer for the newly-launched company, Phylloceuticals.

Being a "pioneer" in flexibility isn't necessary in all cases.

"Even within flexibility you need to take into account flexibility," says a director-level facilities manager at major American pharmaceutical company. "In some cases, if you have a molecule that you know is going to be a blockbuster, that isn't the way you need to produce it. Maybe you do need to look at economies of scale and ways to do that in fixed systems that actually make sense."

But perhaps to the detriment of flexibility, new enabling technologies and award-winning facilities have painted a picture of higher first costs for flexible facilities. Yet, that is not always true and that line of thinking can hold the industry back.

"That is one of the problems. Flexible doesn't need to mean 'new' anything," says Odum. "Often flexibility can be achieved simply by optimizing current operational activities or by using simulation tools to better understand day-to-day needs."

According to Bornholdt, manufacturers should first pay very close attention to overall cGMP

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> **You can make most of the improvements needed to truly make your manufacturing plant adaptable and flexible, without having to spend a whole lot of money."**
>
> — Ken Anthony

facility flows (personnel, product, material, and waste movement) and how re-purposing or expanding will impact day-to-day operations. Moving towards closed processes and considering the appropriate level of segregation between unit operations are also important first steps, he says.

Anthony views it as an 80/20 rule.

"You can make most of the improvements needed to truly make your manufacturing plant adaptable and flexible, without having to spend a whole lot of money to do those things," Anthony says. "I start with a goal of 20 percent additional cost to yield 80 percent greater flexibility."

Most of the proverbial low-hanging flexibility fruit can be captured early on in the facility design project.

"There are things you can do technically to make a facility inherently more or less prone to change and problems," Anthony says. For example:

Building knockout panels in walls

Knockout panels, which are a section of wall that can be removed (or reinstalled) without demolition, enable manufacturers to change plant capacity or move/add equipment as needed.

This essentially embeds flexibility into the walls upfront, and means manufacturers won't incur the costs of demolishing walls and moving existing equipment, pipes and electrical equipment.

"Knockout panels add no additional cost to the base building cost. On the flip side, if the owner decides later to move or add equipment and this was not planned for in the original design/construction, the costs can become exorbitant," says Anthony.

Adding ample ceiling height and clearance

Rather than wrapping the facility tightly around equipment and interior spaces, manufactures can opt to add additional clear height — the distance from the finished floor to overhead objects — to a facility at the start of construction. This will help them avoid a situation down the line where new equipment or processes are needed and the building height cannot accommodate them.

"In this scenario, there is an added cost to the baseline building — maybe five percent more expensive. But the costs to 'stretch' a building after it is built are steep — and usually considered a constraint to proceeding. The opportunity cost in this scenario for the owner can be many times more than the whole cost of the original project," says Anthony.

Bornholdt agrees and says in general, manufacturers should aim to design spaces that accommodate a wide range of equipment vendors and equipment scales.

"Door and corridor clearances, ceiling heights, as well as power

The top 10 global pharma companies are reporting almost $16 billion in construction projects.

—Industrial Info's 2021 Industrial Market Outlook[1]

and utility requirements, should be confirmed against many potential equipment suppliers," he says.

Plan for utility isolation or expansion

Installing appropriate and ample locations for utility isolation, shut-off and tie-in upfront can greatly reduce the operational downtime required for facility modification or expansion.

"Utility, power and data use points can include blank 'stub outs,' 'spares,' and 'rough-ins' that may be filled in the future with little impact to ongoing operations," says Bornholdt.

"There is an added cost here but it means you don't have to shut down sections of the plant — or worse, the entire plant — when it comes time to add/change/provide maintenance on utility equipment," says Anthony.

Additionally, other aspects such as foundation type and capability, floor coatings and HVAC management system configuration should be assessed for their level of flexibility.

Overall, many flexibility benefits can be captured from planning and forethought — without draining pharma's wallets.

A flexvana future

As advances are made in manufacturing facility design, equipment, and processes, pharmaceutical companies are finding themselves

facing an intimidating list of flexibility-related options. At the same time, the nature of the pharma industry itself is evolving, and new modalities continue to change the game for pharma manufacturers.

Fortunately, once the industry pushes past the buzzwords and gets down to logistics, the path to flexibility can be made smoother by establishing clear business drivers, making decisions early, and above all, recognizing that there is no magic flexibility pill.

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Meagan Parrish
Senior Editor

Focus on: India

The world's leader of generic drug production looks toward new horizons in pharma

You don't have to scratch very far under the surface of India's pharma industry before you detect a hint of defensiveness. Have pharma companies in India had some run-ins with quality issues? Sure. But, as many in India's pharma sector point out, when your industry is this big, that's bound to be the case.

While India manufacturers address ongoing quality concerns, Sriram Shrinivasan, the global generics leader and India health sciences leader at EY, says that clickable headlines about U.S. Food and Drug Administration (FDA) warning letters for Indian pharma plants have cast a potentially unwarranted cloud over the country's drug sector. According to Shrinivasan, there's a bit of "hype" involved with how the outside world views Indian pharma manufacturing.

From an insider's point of view, India has a strong track record of successful drug manufacturing with plenty of quality wins to boast about as well.

Home to the world's second largest population, India has more than 3,000 pharma companies and 10,500 manufacturing facilities dotting its landscape, including the largest number of FDA-compliant pharma plants — more than 260, including API facilities — outside of the U.S.

The globe's third-largest exporter of drugs with its success rooted in generic drug production, India is oft referred to as the "pharmacy of the world" — a moniker the industry there takes seriously. And despite becoming a generics giant, India's pharma industry has proven to be nimble on its feet as it meets emerging challenges head on.

India's pharma space has found room to grow by adopting advanced technologies and breaking into rising sectors of the industry.

Market size

India's pharma industry wasn't supposed to swell to its current size. Starting in the 1970s, growth in India's pharma sector was fueled by the Patent Act, which recognized process — but not product — patents, allowing pharma companies to reverse-engineer and produce drugs that were still protected by patents.

But in 2005, India signed on to the World Trade Organization's Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement), which sought to harmonize patent laws across member states. The new agreement forced India

STATISTA RESEARCH DEPARTMENT

to recognize product patents, giving rise to concerns that growth in the industry would ultimately falter.

Rather than losing its edge, India's pharma industry adapted to a more globalized structure and has continued to flourish.

According to Shrinivasan, India's pharma industry was valued at about $4 billion just two decades ago. Today, it's worth more than $41 billion. India's pharma sector is also unique in the sense that its industry is evenly divided between drugs manufactured for export and those made for domestic use by the country's 1.3 billion citizens.

Much of the growth continues to rest on generic drugs. Shrinivasan says that about 40 percent of the FDA's approvals for Abbreviated New Drug Applications — or ANDAs, the applications for new generic drugs — come from Indian companies.

The lower cost of production — about 40-60 percent less than in the U.S., according to EY's estimates — coupled with a steady stream of skilled STEM workers has also made India an attractive destination for pharma manufacturing.

Yet, India's pharma space has also found room to grow by adopting advanced technologies and breaking into rising sectors of the industry — all while navigating what Shrinivasan calls a "perfect storm" of problems.

New threats

Price erosion

"A major issue [for India's pharma industry] is U.S. pricing," Shrinivasan says.

Within the last decade, significant consolidation among buyers in the U.S. has taken pricing leverage away from Indian pharma companies. The consolidation among major retail pharmacies, drug wholesalers and health care institutions has amounted to a situation where three buyers now control about 90 percent of the market for Indian drugs, Shrinivasan says.

As a result of the consolidations, Shrinivasan notes that pricing on generic drugs from India has been decreasing "quarter by quarter."

"This has reduced the ability for Indian pharma companies to make margins," Shrinivasan says.

More competition

While prices continue to fall, the number of new entrants into the industry is on the rise, partly due to a side effect of the FDA's Generic Drug User Fee Amendments law (GDUFA).

Enacted in 2012, GDUFA was designed to speed the approval of new generics to help the U.S. address rising concerns over drug shortages. Prior to GDUFA, Shrinivasan says it could take two to three years to get a new generic drug onto the U.S. market. Now, the timeframe has shrunk to a matter of months.

While the country's major pharma manufacturers — Sun Pharma, Dr. Reddy's, Cipla and others — still dominate the scene, a swath of new and smaller players have sensed the opportunities created by GDUFA and elbowed their way onto the market.

The pharma industry in India is also facing rising competition from other countries, such as Bangladesh, looking to expand high-volume commodity manufacturing for generic drugs.

Supply chain hiccups

Similar to countries around the world, pharma companies in India have found themselves a bit more beholden to Chinese imports of active pharmaceutical ingredients (APIs) and key starting materials (KSMs) than they would like. This reliance on China for the needed ingredients to produce generics has been heightened during the COVID-19 pandemic.

"During the last few months, most countries — including India — have experienced disruptions in the pharma supply chain because of the dependency on China for APIs and KSMs," Shrinivasan says.

Yet, like many countries with a large generic drug production infrastructure, the reliance on Chinese imports has also become a catalyst for change.

Growth factors

API production

Already one of the largest generic drug companies in India — and the world — Dr. Reddy's has set a new, ambitious goal for itself. According to Marc Kikuchi, CEO of Dr. Reddy's North American Generics unit, the company is now looking to become the globe's leading API supplier by 2027.

> **What companies in India haven't done well so far is discovering and developing new molecules."**
>
> — Sriram Shrinivasan

The pandemic was a needed wake-up call for the industry, Kikuchi says. Although Dr. Reddy's, which sells over 150 different product families in North America alone, was able to keep about 90 percent of its portfolio in stock during the pandemic, the company has sharpened its focus on further securing its supply chain in recent years.

One strategy has involved diversifying its sources for APIs to companies in the EU and India — a trend that Kikuchi is seeing throughout the pharma industry in India.

"There are unexpected partnerships emerging in India right now," Kikuchi says. "Evidently companies have been buying APIs amongst each other for a long time, but now some of these companies have progressed to commercializing finished dosage forms in the U.S."

But, like many in the industry, Dr. Reddy's is also pivoting towards producing more of its own ingredients.

"We want to have more control of our supply chain and control of our destiny," Kikuchi says.

Of course, as the entire industry looks for ways to move away from China, Dr. Reddy's is also seizing the opportunity to become the world's new go-to source for APIs.

Currently, Dr. Reddy's manufactures its APIs for North America in Mexico and India. Going forward, Kikuchi says the company could expand its API footprint in India to boost output, while marketing its name recognition and supply reliability to increase its attractiveness over Chinese sources. Even if Dr. Reddy's doesn't land in the No. 1 spot on the global API market, Kikuchi says that expanding its API business will be an important pillar of growth for the company in the years to come.

"Worst case scenario, we're in the top three [for global API suppliers]," he says.

Indian companies looking to expand API production are finding plenty of backing from the local government. As part of a new, two-phased initiative called the Production Linked Incentive Scheme, Shrinivasan says that the Indian government is pouring money into increasing capacity for Indian-made APIs.

"The Indian government has approved a spend of around $2 billion to boost domestic capability in manufacturing APIs and various categories of complex formulations," he says.

Strict environmental laws, however, could slow the rate of investments into India's API and KSM space. According to Sujay Shetty, a partner at PwC India, India has environmental laws on par with first world countries. In this regulatory environment, winning a permit for manufacturing can take up to nine months — a wait period that the industry would like to see reduced to one to three months.

"This is bothering the industry," Shetty says. "They want shorter periods of environmental approval times."

Going forward, India will have to strike a tricky balancing act between demands from environmental groups and the desire for industry investments — particularly for APIs and KSMs, which are often considered "dirty" products to manufacture.

"There is a way to do it without compromising environmental rights," Shetty says. "But it's not a very easy problem to solve."

Going up the value chain

How can Indian generic drug companies stay competitive with new entrants flooding the industry? With novel delivery systems.

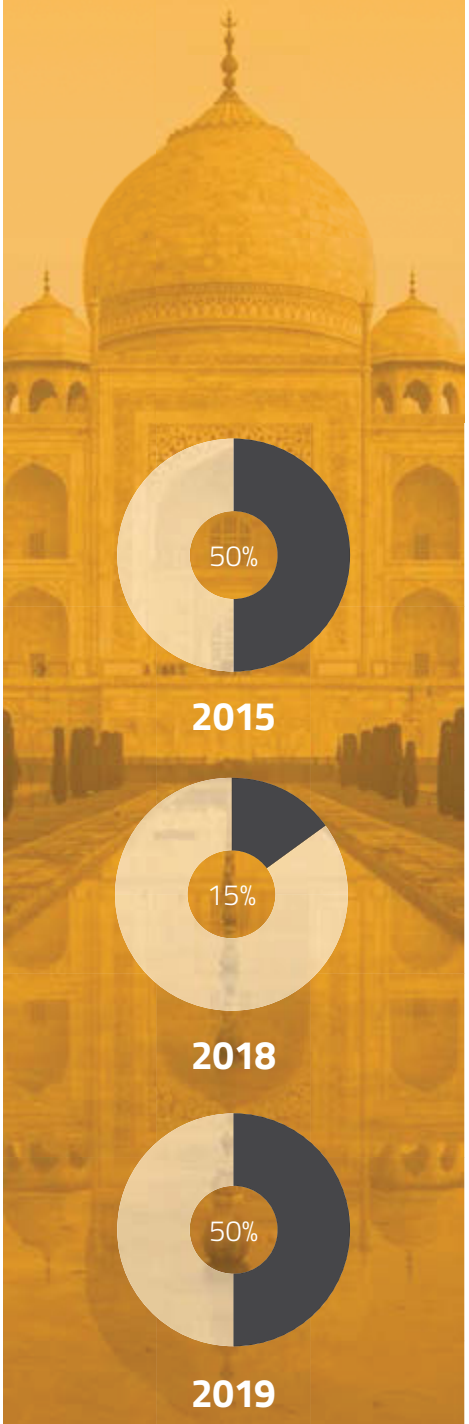
"If something is a tablet, make it into a patch. If it is a capsule, make it into an inhaler," Shrinivasan says.

Embarking on these kinds of changes costs more in R&D, but Shrinivasan says that Indian companies are turning to this strategy more frequently because they can leverage the enhanced value to keep prices competitive.

Biologics and vaccines

In 2017, Biocon became the first Indian company to usher a new biosimilar across the FDA approval finish line. Developed with Mylan, the drug, Ogivri, is a biosimilar to Herceptin, Roche's blockbuster cancer med.

Even before that major FDA win, Biocon had already successfully launched biosimilars in other countries — proving that an Indian pharma company can become a big player in this high-growth sector of pharma. Late last year, Biocon



Quality control

Overall, increased quality measures reduced the share of FDA warning letters from Indian companies in the last five years. In 2015, about half of all of the FDA's warning letters went to India. In 2018, that share plummeted to 15 percent — although it rose again in 2019 to about 50 percent.

Biologics, the company's biologics subsidiary, also scored a $150 million investment from Goldman Sachs.

"Recent deals demonstrate the confidence that large global institutions have in India's ability to become a world leader in biosimilars," Shrinivasan says.

Vaccines are another frontier where Indian companies are showing their prowess. According to Shrinivasan, over 60 percent of the world's vaccines come from India — and it's a role that has become more vital during the pandemic.

In January, Indian regulators approved Covaxin, a COVID-19 vaccine developed by Bharat Biotech, a local company that received government backing. Phase 3 trials of Covaxin showed that it was about 81 percent effective and the company has plans to export doses to a number of neighboring countries.

India has also approved the vaccine co-developed by University of Oxford and AstraZeneca, which is being manufactured by the Serum Institute of India (SII), the world's largest vaccine maker. Prior to the pandemic, SII cranked out about 1.6 billion doses of vaccines annually, distributed in over 170 countries. Now, SII says it is making more than 50 million doses a month of the Oxford/AstraZeneca vaccine.

Innovation

"Every year there are literally millions of engineering grads coming out of the school system, so you have plenty of qualified people," Kikuchi says about one of the prime benefits of manufacturing in India.

This constant flow of science-minded grads not only helps keep the pharma industry humming, it will also be critical to companies hoping to innovate new drugs — an area of pharma where India has yet to thrive.

"What companies in India haven't done well so far is discovering and developing new molecules," Shrinivasan says. "The holy grail now is to get into the innovation game. They haven't got that right yet, but they are working on it."

In addition to more companies discussing increased R&D investments, Shrinivasan says the government has also set up a new venture capital fund that provides seed money for drug innovation.

Onwards and upwards

Quality issues may continue to haunt the Indian pharma world, but for the industry there, that challenge has also provided more incentive to push towards the adoption of advanced technologies.

"In the past few years, [Indian pharma companies] have realized that the new nucleus on value creation lies at the heart of digital transformation, which has been further intensified during the COVID pandemic," Shrinivasan says. "Leading generics companies across India have started implementing automation and digitization across the value chain, including R&D for faster approvals and reach, supply chain planning and optimization tools, and quality planning tools to reduce anomalies."

For Dr. Reddy's, which received five Form 483s from the FDA in 2019 for various quality observations, being dinged by regulators has offered more opportunities to fine-tune processes. In particular, Kikuchi says one strategy Dr. Reddy's has used is closely monitoring what other companies are being issued observations for — such as documentation or cleaning procedures — to stay on top of regulatory trends.

The company has taken steps to beef up its quality management in the last few years by revamping procedures, implementing new analytical methods to better detect impurities, and leveraging artificial intelligence and digital analytics for better data management in the production process.

"It's all about continuous improvement," Kikuchi says.

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Joe Reckamp
Analytics Engineer, Seeq Corporation

Deploying advanced analytics for predictions

Why proactively predicting required maintenance is a better approach

Advanced analytics in the pharma industry is a problem-solving journey through historical, current and predicted data, with insights driving an improved decision-making process.

Efforts typically begin with a monitoring focus, concentrating on the most recent operations data available, with a goal of quickly identifying and surfacing issues. As an organization's analytics efforts increase, it often starts to leverage historical advanced analytics as well, diving into the terabytes of data stored in historians or other databases to fine-tune insights. Using a process often referred to as diagnostic or root cause analytics, subject matter experts (SMEs) can explore recent issues, such as a deviation during the previous batch, or long-term issues, such as the frequency of failures of agitator bearings over the past decade.

With historical advanced analytics, the goal is leveraging stored data to inform process changes that can be made to improve operations. These changes may be focused on preventative maintenance or mitigation strategies, each to reduce process deviations or equipment failure. Other goals may include optimization initiatives, such as a change to process setpoints to match historical batches that produced the highest quality or yield.

Leveraging historical data shifts an organization from simply monitoring and reacting to issues as they arise to using data and context to better inform process improvement decisions. While historical advanced analytics are useful in finding and eliminating common issues, this type of process improvement is still inherently reactive in nature, meaning that an issue must occur in the past to be investigated and prevented moving forward.

Fortunately, there is a way to anticipate some problems before they occur, enabling the implementation of proactive solutions.

Back to the future

For certain asset or process failures it may be possible to completely avoid the issue in the future by, for example, adding a cleaning step to remove contamination. But in many situations, the failure may be due to equipment performance degradation or other foreseeable causes, making it critical to shift the historical analysis into predictive analytics.

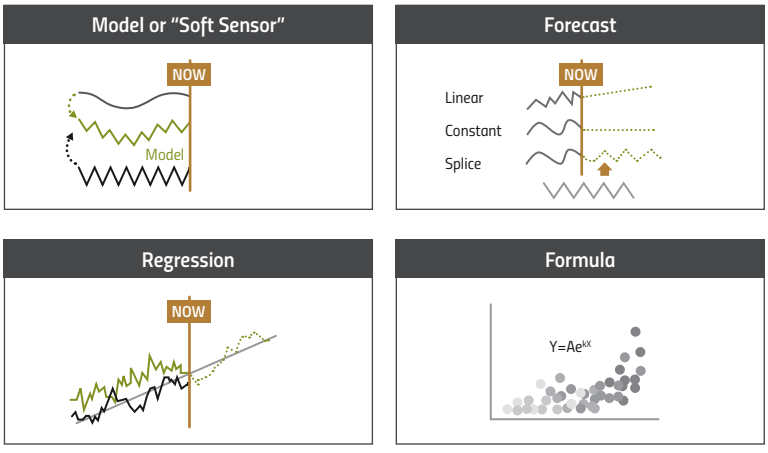
Predictive analytics represents a type of advanced analytics that leverages historical data for building and training a model to create a projection of expected future data (Figure 1). Common use cases of future data in manufacturing applications are equipment-based predictions, also known as predictive maintenance, where the goal is to anticipate when equipment requires maintenance or will fail.

Other common use cases include process-based predictions, where the goal is to optimize the process by modeling product quality, optimizing process setpoints or acting as a soft sensor for parameters not easily measured. In equipment and process scenarios, historical data for the equipment or process is analyzed to train an algorithm to project future data based on a set of constraints and assumptions.

FIGURE 1

Quantification models

Models are created using advanced analytics software and then used to predict problems.



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Categorization versus quantification

Predictive maintenance techniques often differ based on the type of equipment and its typical failure mode or event, but the purpose of the predictions remains constant: to increase quality, reliability and uptime.

Predictive model creation starts with determining the best technique, either categorization or quantification. Categorization models use classification and clustering algorithms to assign a category to each section of the data, which often corresponds to distinct operating modes.

When using a categorization technique for predictive maintenance, data is usually assigned to normal or abnormal operation categories, where abnormal operation indicates a potential imminent failure. While categorization models can be useful in specific applications, quantification models are generally preferred because they provide enhanced granularity related to equipment health.

Predictive analytics leverages historical data for building and training a model to create a projection of expected future data.

For example, instead of an algorithm sounding an alert to indicate equipment performance has gone awry and failure is imminent, a quantification model can provide the current rate of equipment degradation to inform the time frame for required maintenance. With quantification models, regression algorithms train or fit a numerical equation or model to relevant historical data. These models can then be utilized to predict future data, from which insights can be created.

Quantifying with first principles

Quantitative predictive maintenance models fit an equation to an available data set. The input data set usually includes a time variable, which counts the runtime from the previous maintenance event, along with one or more process parameters. Process parameters may be raw tags from a data historian or calculated tags created using advanced analytics, such as a calculated principal component representing several input variables.

The preference is to develop models using first principles equations corresponding to equipment performance. These first principles calculations can correspond to a wide array of phenomena including pressure drops, internal friction, or thermal efficiency based on established laws, principles and theorems. With this method, data can be dimensionally reduced and fit to the appropriate regression algorithm, while minimizing the amount of training data required.

Once the model is trained on historical data, it then needs to be forecasted into the future, requiring all inputs to the model to be forecasted. Several forecasting options are available. For continuous processes it is common to forecast that the future value will likely be the same as the average value from the previous day or week. For batch or transient processes, the modeling process is more complex and may include regression calculations or average daily or batch profiles.

Once all the inputs to the model have been forecasted, the outputs of the model can be used to determine the projected maintenance period by alerting when a critical value on the model forecast has been reached. The critical value for maintenance may be defined by subject matter expertise, vendor specifications, through an analysis of historical failures or issues, or a combination of these efforts.

Predictive maintenance case studies

One example of using first principles equations for predictive maintenance in the pharma industry is to detect fouling or degradation of heat exchangers and filtration membranes. Heat exchangers are used on the process contact side as jacketed tanks and condensers, as well as on the utility side for equipment such as steam generators or cooling towers.

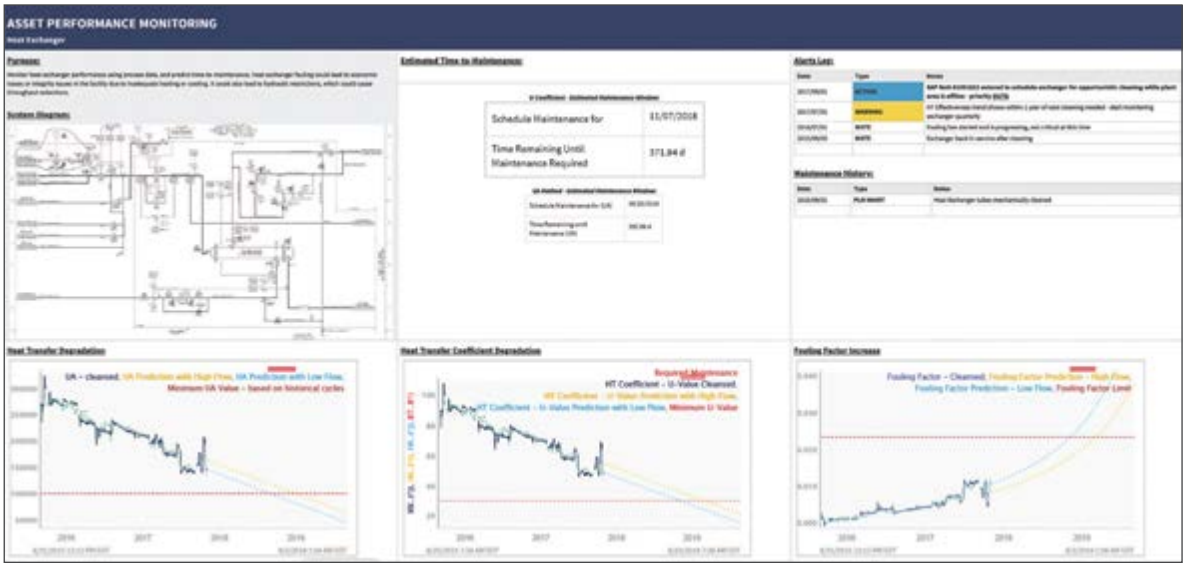
While the process contact side of the exchanger may be cleaned and inspected regularly, utility applications are often run for extended periods of time. Although typically considered to be clean services, they may contain impurities or sediment due to the buildup of scaling or fouling over time.

Heat exchanger efficiency and performance is quantified using

FIGURE 2

Asset performance monitoring

This heat exchanger predictive maintenance model provides a wealth of information with respect to present and future equipment condition.



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the heat transfer coefficient based on the First Law of Thermodynamics. This coefficient is derived from the flow rates, temperatures and physical constants such as the exchanger surface area. Use of the heat transfer coefficient effectively reduces the dimensions of the model from six tags (four temperatures and two flow rates) to a single performance parameter. This technique has been extremely successful when models are paired with data cleansing techniques that focus on areas of steady state flow.

Similarly, filtration membranes, which are found throughout the process and utility sides of pharma plants, foul and degrade over time. Filtration membranes can be simplified to a membrane resistance value using Darcy's Law, which considers flow rates and pressure readings on each side of the membrane, along with constants such as the filter area and fluid viscosity. After reducing to a single performance metric, the trend between maintenance cycles can be modeled as a function of time and other process parameters.

Most models only require linear regression, but more advanced techniques may be required. For example, polynomial or exponential regressions may be incorporated based on subject matter expertise regarding the failure mechanism or the empirical fit of the historical data. Outputs of the statistical analysis, such as p-values, help identify the parameters having minimal impact on the predictive model, which can then be removed to reduce complexity and noise. Finally, the regression model can be forecasted or extrapolated into the future based on expectations of the inputs in the future, and it can create alerts when the model output reaches a critical value.

The goal of process-based prediction models is predicting a critical quality attribute.

Figures 2 and 3 show predictive maintenance models built using an advanced analytics application, for heat exchangers and filter membranes, respectively. Heat exchanger operation is typically a continuous process and was therefore assumed to have a range of process conditions, so a low and high estimate were forecasted. Filter membrane operation is typically a batch process, so the model forecasted the same frequency of batches as in the past to create insights.

Process-based predictions

Process-based prediction models, also known as predictive quality models, follow a similar approach as predictive maintenance models, but the goal is changed from modeling

FIGURE 3

Filtration membrane resistance

Filter membrane performance can be predicted with models primarily relying on membrane resistance.

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equipment performance to predicting a critical quality attribute (CQA), such as potency or yield.

While first principles formulas may be available for certain applications such as reaction kinetics, process-based predictions tend to focus on empirical models derived from design of experiments or numerous production runs. Benefits of process-based predictions can be achieved in both batch and continuous operations by identifying optimal process conditions, reducing cycle times and providing real-time insight into the process — all without waiting for sample results.

Reactive to proactive

Many pharmaceutical processes are run on a reactive basis, with plant personnel dealing with issues as they occur. A better approach is to proactively predict problems before they occur as this provides a number of benefits including lower maintenance costs, increased uptime and improved quality.

Frederick Murray
President, KORSCH America Inc..

Back-to-basics on tablet press efficiency

How an objective assessment of equipment's efficiency can make a big difference

As the pharma manufacturing industry continues to increase its focus on optimizing operational efficiency, high-volume tablet production should not be an exception.

In many instances, there is a tendency to investigate new trends or developments in automation and the fundamentals — the basic blocking and tackling of efficient tablet production — are overlooked. But in most production environments, there is potential to materially improve overall efficiency by focusing on the key parameters that drive overall equipment effectiveness (OEE); namely, production output, yields, uptime and labor requirements.

Here, we will take a back-to-basics approach to highlight actionable improvements applicable to any solid dose production environment.

Optimizing tablet press output

For most tablet products, the press speed range, including maximum press speed, is defined in the process validation protocol. Considering this, any effort to increase production speeds must incorporate an understanding of this constraint. While the press speed range should have been established on the basis of process capability, in some cases the values are historic.

Knowing this, assessing the current process capability is always a good place to start determining how well the process is under control, and what the potential is to increase turret speed (and therefore production) while maintaining critical quality attributes.

The process capability (C_p) can be calculated for tablet weight, thickness and hardness for any product, as follows: $C_p = (USL - LSL) / 6 * \sum$

Where:

C_p = process capability index
USL = upper specification limit
LSL = lower specification limit
$\sum$ = standard deviation

Nominal process capability values of 1.33 or 1.50, or higher, are generally indicative of a process that is under control, and process capability indices of greater than 2.0 would suggest that an increased press speed is possible while maintaining process quality. Increasing press

speed will decrease both feeder dwell time — the time that the punches are beneath the feeder — and compression dwell time, which is the time it takes for the punch head flat to travel across the compression rollers. This means higher press speeds have the potential to create expanded tablet weight variation due to reduced die fill time, as well as lower tablet hardness due to a shorter dwell time in which compression force is applied.

If it is possible to increase the press speed within the validation process range and maintain an acceptable level of process capability, then this is a logical first step toward optimized press efficiency.

A second option for materially increasing output performance comes with leveraging multiple turrets to maximize output for every tablet size. Most modern production machines offer a series of interchangeable turrets. With knowledge of the different tooling sizes and standards, the selective use of multiple turrets can have a considerable impact. (See sidebar)

By aligning tablet size to turret selection, the output can be maximized across the product portfolio without increasing the validated speed range. In addition, the use of multiple turrets — which entails the potential to clean, prepare and tool turrets offline for fast change — also can have a material impact on efficiency by significantly reducing overall downtime.

Maximizing tablet press yields

Across all batch sizes, a clear, consistent objective is to maximize the number of good tablets that can be produced while minimizing inevitable product loss. In general, product losses can be categorized as follows:

- Startup scrap
- In-process losses
- Sampling losses
- Batch end scrap

For most products — and those with highly potent APIs in particular — it is necessary to generate a complete reconciliation to account for the total batch weight. This means the total of all loss sources plus the total good tablet weight must align with the total starting weight of the batch. For most modern tablet presses producing a single-layer tablet, production yields in the range of 95-99 percent are achievable.

Startup scrap is generated when the machine is being setup with process parameters to achieve the required product weight, thickness and hardness. Often, and certainly at higher press speeds, considerable losses can be generated if the operator must make an iterative series of adjustments before settling upon the proper settings.

The best way to minimize startup scrap is to utilize a product recipe capability in which a comprehensive list of optimized machine parameters is stored and retrieved automatically. Most modern tablet presses offer such a capability; one where the product recipe system will automatically configure the tablet press, including settings for press speed, dosing position, tablet thickness, press force settings, punch lubrication system settings and sampling/parameters settings for an inline tablet tester.

In-process losses include material lost from the feeder and either recovered or not recovered in the dust collection system. Most modern tablet presses have advanced feeder seals designed to maximize production yields. These seals eventually wear out and require replacement based on the processing parameters and the nature of the material being produced. The granulation particle size also can have an impact, as fines will always be harder to contain in the feed frame. In addition to inspecting and intermittently replacing feeder seals as required, the dust extraction volume — the amount of air pulled from the compression zone through dust extraction nozzles — is also a critical parameter. In many applications, the tablet press is connected to a central house dust extraction system, and the dust extraction volume can be impacted by the number of machines connected at any given time.

Especially in these instances, it is beneficial to install a sensor to measure the dust extraction pressure in the compression zone or dust extraction main duct and to maintain this indicator at an optimal level that ensures extended operation and minimal material losses. Many modern tablet presses offer an integrated system that includes a pressure sensor that monitors dust extraction and allows control of a motorized damper for consistent, optimized dust extraction volume independent of factors elsewhere in the plant.

In-process losses also can come from tablets rejected by the control system over the course of the batch. Most advanced control systems include an automatic tablet rejection capability permitting single tablets, or a group of tablets, to be rejected based on compression force. Individual compression forces that violate preset upper and lower limits allow tablets to be rejected across the speed range of the machine. In general, these systems are intended to identify and reject outliers associated with a poor die filling or overfilling of the dies with fines.

If the tablet rejection system is working constantly, then the process is clearly not in control and adjustments to the machine setup, including a reduction in press speed, may be warranted. Most single-tablet rejection systems

Typical turret options for a modern, single-sided rotary press

Per the various press tool standards, it is critical to understand that the EU/TSM B, the EU/ SM BB and the EU/TSM BBS press tools are identical – only the die diameters are progressively smaller. With identical upper and lower punch tool geometry, the compression dwell time is equivalent at the same press speed for these tool sizes. The feeder dwell time is also the same, since the punch is traveling at the same linear speed across the same feeder opening.

For example, a 10 mm diameter tablet running on a TSM B turret with 35-stations at 80 RPM will produce 168,000 tablets per hour. If the same tablet is produced at the same press speed with a 47-station TSM BBS turret, the output becomes 225,600 tablets per hour, an increase of 34 percent. The ROI on the additional turret and transport cart is then a simple calculation – and typically well worth it.

Turret specification	Number of stations	Maximum tablet diameter
EU or TSM D	29	25 mm
EU or TSM B	35	16 mm
EU or TSM BB	44	13 mm
EU or TSM BBS	47	11 mm

are complemented by an electronic audit trail capability that tracks the number and source (punch station) of the tablets being rejected. Excessive rejects from the same punch station can point to a problem with the press tooling — such as picking, sticking or damage to the face of the tool — that can be resolved by replacing the affected punch station.

Sampling losses occur based on sample size and frequency. Certain advanced presses offer the capability to sample on demand from the HMI, which, based on press speed, will provide a sample of the appropriate size with minimal losses. Sampling to an automated tablet tester for tablet weight, thickness and hardness measurement can automate the sampling process, but is unlikely to have any material impact on the magnitude of sampling losses, which are typically very minor.

Most advanced presses have a low material level sensor that will stop the machine when the material is almost empty; typically, there is material remaining in the feed pipe above the feeder. Depending on the volume of the feeder and the geometry of the feed pipe, some machines offer the ability to override the low material level sensor and run the press under automatic control, producing an incremental quantity of good tablets for as long as the remaining material quantity will support. In this case, the low average compression force alarm will eventually stop the machine before any reject tablets are produced. For exceedingly small tablets, the incremental quantity of good product produced after the initial low-level alarm can be considerable, adding favorably to overall production yield.

Increasing production uptime

To provide the basis for uptime improvement, it is first necessary to understand the sources of downtime. Most advanced production control systems are equipped with electronic audit trails that track both machine adjustments (event log) and machine diagnostics (alarm log). An analysis of the alarm log will permit an assessment of those faults causing the machine to stop, such as punch tightness or violation of press force limits. Analyzing the faults' frequency offers an opportunity to execute a remediation plan. For example, frequent machine stops due to punch tightness may be resolved by increasing lubrication to the upper or lower punches — a simple adjustment made via HMI.

The review of machine alarms can be complemented by an understanding of what adjustments are being made to the machine by the operator over the course of the batch, which is generally captured in the event log. The event log provides a time-stamped log of all machine adjustments and includes the operator of record, the before value and after value for each parameter. In some cases, incorrect adjustments might be occurring that make the process unstable — or that result in faults causing machine stoppage. When reviewed together, the alarm and event logs can provide insight into what is happening at all times, and can identify training deficiencies and remedial actions that have a dramatic impact on overall efficiency.

Once the batch is finished, there is a major emphasis on changeover time. To start, the cleaning and changeover requirements must be carefully defined. For example, producing the same product at varying strengths may require a different procedural approach than switching to a completely different product and active material. In general, the changeover sequence for a tablet press includes the removal of all product contact parts, the removal of the press tooling, and the cleaning of the press and related peripherals, followed by the installation of new press tools and clean product contact parts. For some machines, this process can take eight hours or longer; however, there are several practical ways to reduce this changeover time.

First, the use of uniform change procedure, and a cart specifically designed to house the product contact parts, can ensure a streamlined and consistent procedure to remove the parts in the proper sequence and place them in a repeatable position. The procedure is then reversed when installing the clean product contact parts back in the press, complete with a regimented SOP, sequence and on-cart part position. To reduce overall change times, some companies employ the use of a second

The KORSCH XL 400 Tablet Press parts cart facilitates a repeatable and fast changeover process.

set of product contact parts, which is cleaned off-line and available immediately when the next batch is finished.

Further, the manual removal and installation of press tools in a turret mounted in the press can be eliminated with the use of an additional turret strategy. Not only can the turret for the next product be tooled off-line (while the press is in operation), the turret configuration can be adapted to the tablet size to maximize production output. Leveraging an additional turret strategy in combination with a second set of product contact parts and a regimented, streamlined change procedure can reduce overall changeover time by 50 percent and condense the process to something less than three to four hours.

Time, of course, is product: More efficient changeovers have an immediate and substantial impact on overall equipment efficiency.

Strategies for semi-attended operation

While leveraging the latest in tablet press automation can certainly present opportunities for improved operational efficiency, this back-to-basics approach should be considered the first course of action. Automation strategies can support a plan to move to semi-attended operation, where a single operator can monitor and operate a number of tablet presses concurrently. First, most advanced control systems permit a configuration where a second HMI may be mounted outside the compression suite, eliminating the need for operators to be present in the room at all times. It is possible to populate a single HMI with a control system overview of multiple machines, allowing the operator to monitor the process remotely on one or multiple machines from outside the compression suite.

Most high-speed tablet compression suites utilize a post hoist, mezzanine or feeding from a second floor, and there is no manual scooping of material into a product hopper. This means that material is fed consistently to the tablet press and no operator intervention is required, at least until a drum or IBC change is required.

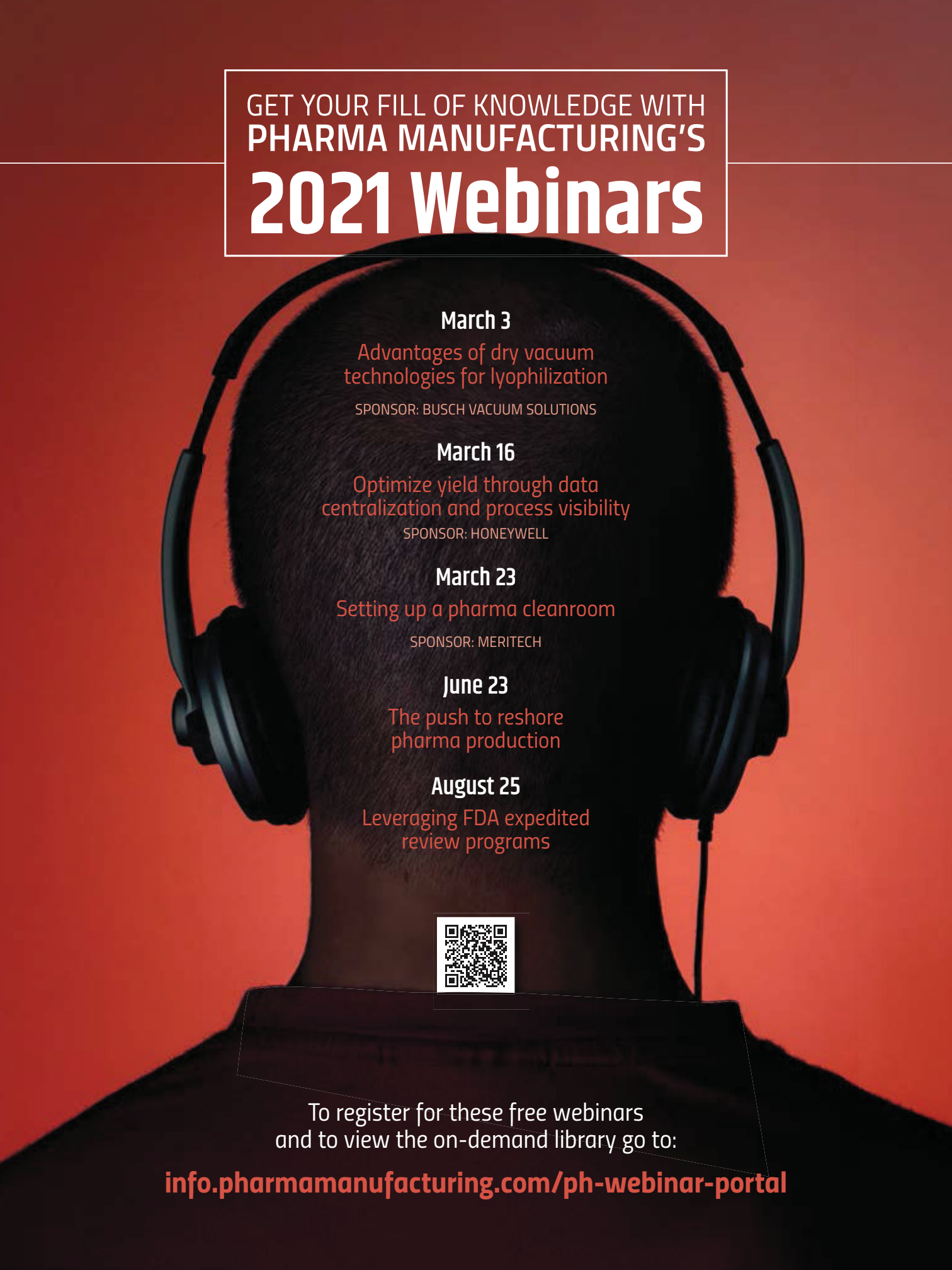
In many applications, a full-time operator presence is required in the room to monitor tablet collection and manually replace full containers to permit the press to run continuously. Most modern deduster and metal check combination units offer a lifting height and a tablet diverter that supports the automated feeding of a large IBC or multiple, smaller containers based on a preset tablet count. Based on the container size, these systems can eliminate the need for the operator to manually manipulate collection containers over a period of several hours; and if the operator is not back in time, the press will simply stop when the last container is filled.

More efficient changeovers have an immediate and substantial impact on overall equipment efficiency.

Another opportunity to achieve semi-attended production is through the integration of an inline tablet tester, which will measure tablet weight, thickness, and hardness of individual tablets at preset intervals, and provide closed loop feedback to the press force control system to keep the process centered on the tablet weight target. In most applications, the values for thickness and hardness are monitored without closed loop feedback, and the press will be stopped if the corresponding average or single value limits for tablet thickness and hardness are violated. Tablets are generally conveyed from the discharge chute by gravity or a venturi system, in which a stream of air is used to transport the tablets to a collection hopper on the tablet tester. The key limitations of these systems are the capital investment required and the ability of automated testers to properly align every tablet shape and size in a repeatable fashion for consistent hardness measurement. While significant advances have been made regarding alignment capability, certain elaborate tablet shapes still present challenges.

In general, a tablet compression system that can manage tablet collection and periodic sampling with closed loop feedback opens the door for semi-attended operation, in which a single operator can oversee and monitor the operation of multiple tablet presses concurrently.

An objective assessment of any tablet press' production efficiency will, in most cases, identify opportunities for improvement and focus on the fundamentals of maximizing output, minimizing product losses, and streamlining changeover times. For most, transitioning to a semi-attended capability is a secondary consideration, once the foundation for high operational efficiency has been established. In cases where existing tablet press technology is especially old, the analysis may conclude that a single, advanced tablet press — one in which output and uptime may be maximized through the active use of multiple turrets and that offers the inherent flexibility to produce single- and multi-layer tablets — can replace multiple older machines that lack sufficient flexibility or fast-change design.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Overcoming obstacles to drug absorption

Technology selection for improving oral bioavailability

Low aqueous drug solubility in the pharmaceutical pipelines is a pervasive issue. In particular, rapidly growing therapeutic areas such as oncology, antivirals and anti-inflammatory indications are largely plagued by low solubility.

As a result, a number of enabling technologies have been developed to improve oral drug absorption and bioavailability (BA). Salt formation for solubility enhancement is a common technique used during solid form selection for ionizable compounds.[1] However, many salts form hygroscopic materials that can lead to both physical and chemical stability issues. In addition, many salts do not substantially enhance a poorly soluble compound's bioperformance because of precipitation of the compound in the presence of food (increased pH), common ions in the stomach or as the pH increases upon transfer into the duodenum.

For the more than 50 percent of the compounds in development that are either not ionizable or suffer from stability issues as a salt form, alternative solubility-enhancing technologies are needed.[1]

Many technologies have been shown to enhance drug BA; however, the most notable commercial products are those that utilize lipid-based technologies, amorphous solid dispersions and micronized crystals. The commercial precedence of these key enabling technologies supports their continued utilization in addressing compounds that are either poorly soluble or poorly soluble and poorly permeable, which may be as much as 90 percent.[2]

Those working in the field will, of course, recognize three important facts:

- The diverse needs of all drug compounds currently in development cannot be addressed by a single enabling technology;
- Development success is more likely if a technology is appropriately matched to the compound properties and product needs;
- Correctly selecting the solubility enhancing technology and predicting clinical outcomes in early-phase programs is critical to avoid re-work/re-formulation in later phases of development.

In many cases, more than one technology can be utilized successfully, and commercial considerations such as desired dosage format (e.g. tablets vs. capsules) can play a decisive role. Additionally, some technologies may suffice for phase 1 studies but not for later-phase clinical studies. Drug developers may benefit from increased awareness and understanding of these considerations and how they can influence efficient technology selection and accelerated pharmaceutical development.

Physicochemical obstacles to oral bioavailability

Physicochemical obstacles to oral drug BA include low aqueous solubility (a thermodynamic property) and a slow rate of dissolution (a kinetic property). Low drug solubility can limit the maximum drug concentration in the small intestine and, therefore, drug absorption. That's because a high concentration

gradient between drug in the intestinal lumen and drug in the intestinal wall is required to drive passive diffusion across the intestinal membrane. A slow dissolution rate is nearly always associated with low drug solubility, and it is compounded in instances where drug surface area and/or diffusion rates are also low.

Low aqueous solubility is a property common to drugs that are Class II and IV of the Biopharmaceutical Classification System (BCS). Factors underpinning the property of low solubility[3] include:

- A high crystal lattice energy (which generally increases with increasing melting temperature of a compound)
- A low energy of aqueous solvation (which generally decreases with increasing Log P value of a compound, i.e., lipophilicity), often referenced as "grease-ball" type compounds
- A combination of both, where the impact of a high crystal energy on solubility is exacerbated by a low solvation energy, often referenced as "brick-dust" type compounds

Through an appreciation of these obstacles, developers may rationalize the principal means by which enabling technologies increase solubility and dissolution rate, namely by either reducing the drug lattice energy, increasing available drug surface area, and/or increasing the energy of solvation.

To aid this distinction, Figure 1 provides a simplified separation of key enabling technologies according to the primary mechanisms of solubility/dissolution rate enhancement. For example, nanocrystals can increase dissolution rate by increasing available surface area of drug. Spray drying and hot melt extrusion (HME) solid dispersion approaches are able to increase apparent drug solubility and, therefore, dissolution rate by isolating the higher energy amorphous form.[4] Lipid-based technologies are effective in augmenting drug solubility as dispersed and digested lipid components mix with endogenous bile salt and phospholipid so that it is more favorable to dissolving the drug.[5]

In many cases, however, clear distinctions cannot be made. Some technology approaches have the capability to increase drug solubility through both solid-state and solvation effects.

Biological obstacles to bioavailability

Overcoming the physicochemical obstacles to low absorption may not yield the desired BA. In these cases, biological obstacles to exposure may be apparent[6] and may include:

- Efflux of absorbed drug back into the intestinal lumen
- Pre-systemic drug metabolism in the intestine
- Extensive hepatic first-pass drug metabolism
- Low passive intestinal permeability

Certain enabling technologies may have the capacity to attenuate these biological obstacles to drug BA, particularly by reducing efflux and metabolism in the intestine. Fatty acids and nonionic surfactants commonly used in lipid-based technologies have frequently been shown to inhibit P-gp and BCRP efflux transporters in intestinal cell models[7] or increase transcellular permeability.[8]

Defining the product needs

Besides physicochemical and biopharmaceutical properties of a compound, there are a number of other considerations that typically affect technology selection for a particular application. These considerations include target dose, preferred final dosage form and size, frequency of administration, specific storage and/or packaging requirements, and excipient acceptance. In some cases,

FIGURE 1

Crystalline compound aqueous solubility

Graphic plotting crystalline compound aqueous solubility with respect to Log P for a range of compounds previously developed into SDDs (squares) or lipid formulations (circles).

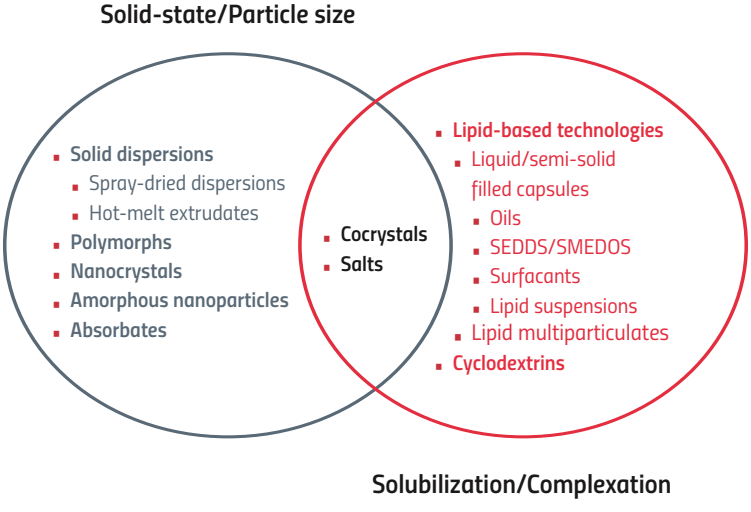
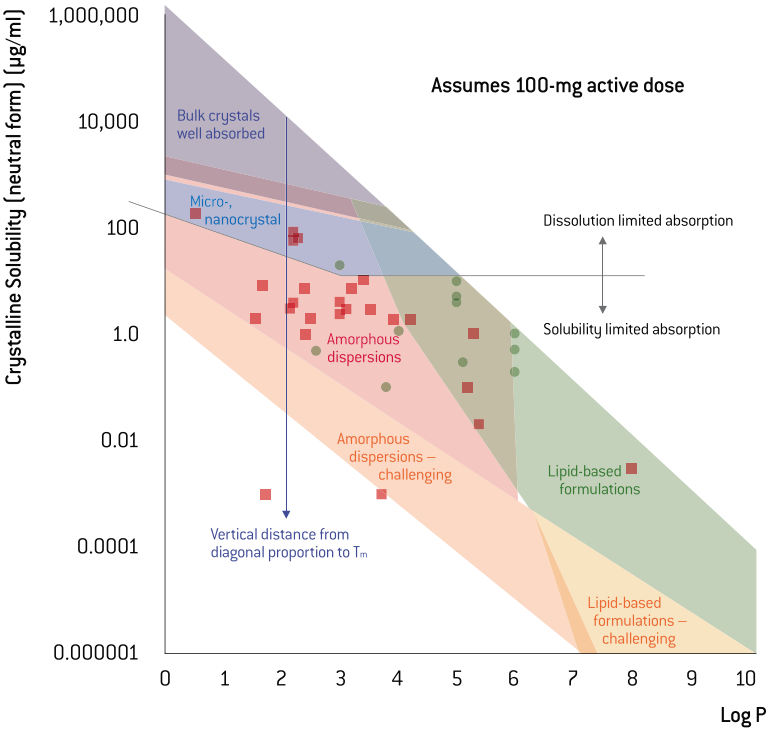


FIGURE 2

Concept technology map based on compound physicochemical properties at a fixed dose

Simplified diagram illustrating the principal mechanisms by which various enabling technogies increase drug solubility/dissolution rate to lead to improved oral absorption.



these factors play an important part in the technology selection process. It is, however, important to note that many if not all of these "technology restraints" can often be identified prior to the initiation of development work, and such considerations can therefore prove valuable by reducing the risk of pursuing certain technologies that are later deemed to be unsuitable.

From a fundamental understanding of enabling technologies, two additional dimensions may aid in the technology selection process: predictive physiological-based pharmacokinetic (PBPK) models and technology maps.

Firstly, PBPK models predicated on modeling mass-transport are also consulted to ratify technology selection since they can be used to predict pharmacokinetic (PK) performance based on compound and formulation properties. These models are based on the fact that an increase in the concentration of all drug species — dissolved free drug, drug in micelles and various undissolved particulate but "high-energy" forms — will, in turn, increase the extent of intestinal absorption of a poorly water-soluble drug.

Secondly, conceptual "technology maps" centered on how key physicochemical drug properties impact oral absorption may be useful. One such example of a technology map is illustrated in Figure 2. In this graph, compound solubility in aqueous media is plotted with respect to Log P. The solid diagonal line in this map traces the maximal solubility of the lowest-energy, neutral form of the compound. Decreasing aqueous solubility at a constant Log P value therefore is driven primarily by an increase in the overall solid-state interactions, which is directly proportional to compound melting temperature (Tm).

In the upper region of this map, crystalline solubility is sufficiently high that bioavailability of a 100 mg compound dose is sufficient when using non-enabling formulations. With increasing Log P and/or increasing Tm, however, the decrease in solubility creates the need for enabling technologies to maintain good in vivo performance. Particle size reduction technologies can offer acceptable BA at a 100 mg dose when solubility falls below 1 mg/ml. However, this tends to result in the dissolution rate failing to maintain the drug concentration at its equilibrium level while it is being absorbed. As the solubility decreases to the range of 10-100 µg/ml (depending on the Log P of the compound), the utility of such technologies will typically diminish. At these low solubilities, it is necessary to utilize technologies that improve drug concentration in the GI lumen above its equilibrium solubility and/or drug transport across the unstirred water layer via sub-micron colloids. Amorphous solid dispersions are highly effective across a broad Log P 0-6 range, but above this range the additional functional excipients provided by lipid technologies are often necessary to solubilize and enhance transport of the compound through the aqueous boundary layer. Lipid technologies also cover a broad Log P 3-10 range, hence there is a progressive overlap region of amorphous and lipid approaches between Log P 3-6 values.

This technology map provides a simplified, two-dimensional insight into how drug physicochemical properties can affect

the feasibility and performance of various enabling technologies. However, this map cannot be utilized in isolation as it does not consider other important properties such as biological obstacles to drug absorption. Additional technology maps that evaluate other properties may be used in combination to aid in technology selection.

Conclusions

Drug development remains plagued with low solubility and poorly bioavailable compounds. While numerous technologies have been developed to enhance these compounds' absorption, three technologies — namely particle size reduction, amorphous solid dispersions and lipid formulations — have emerged as the leading technologies in the field.

By considering the physical and biological factors limiting absorption, the fundamental science behind the technologies and PBPK models, drug developers can identify the appropriate technology to achieve sufficient BA and meet target product profiles. Technology maps, based on historical analyses of key API parameters, can simplify and accelerate technology selection. As the small molecule pipeline continues to contain compounds with low BA, and accelerated development timelines become the norm, a sophisticated understanding of the range of appropriate enabling technologies will become even more important for innovative drug development.

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Spencer Fisk
Chief Technical Operations Officer, Rubius Therapeutics

From the ground up

Lessons from building a new biomanufacturing facility in a year

The global biomanufacturing market is expected to reach $43 billion in the next decade as large-scale manufacturing for biotech and pharma products remains a critical aspect of delivering life-changing medicines. The ability to get a manufacturing site up-and-running quickly and efficiently is vital to companies that want to remain competitive.

Our team at Rubius Therapeutics was able to revamp and operationalize a new manufacturing site for an investigational therapy that had never been manufactured in a cGMP environment in record time — one year ahead of schedule — at our site in Smithfield, Rhode Island. Here are some of the key lessons we learned.

Location and talent

When choosing a manufacturing site location, it's important to consider current and future physical space needs. Once the optimal footprint is selected, it comes down to location. Identifying areas that can fuel growth in the short term and allow scalable manufacturing capabilities to be developed over time will ensure success in the long term. Proximity to your company's development team is also important — interaction and collaboration between development and manufacturing teams is key, particularly when establishing an entirely new platform.

When choosing a site, companies should consider not only the local life sciences ecosystem, but also manufacturing expertise within the state. The best locations will supply support from all types of partners, from complementary companies to local officials. A connected local business community provides partners for infrastructure development, enhancements to the supply chain and other essential business functions.

Following the acquisition of our Smithfield facility, we engaged several organizations to lead the renovation and build on a two-year timeline. Efficiencies on the part of all parties involved, including local partners, led to a completed build out nearly a year early, which underscores that choosing the right partners can lead to success.

When manufacturing new or complex therapeutics, the right kind of workforce is also critical.

Rhode Island proved an ideal location with access to existing high-caliber talent across the Providence region. Local workforce development programs, such as RI BIO's Leadership and Development program and the RI Chamber of Commerce's Wavemaker Fellowship, provide public-private partnerships that give companies the ability to train and attract employees in a way that fits business needs. The right mix of talent factors allows for team growth at a fast pace — our team in Smithfield grew from three to 71 employees in less than 18 months.

To outsource or to own?

Company-owned manufacturing operations is an emerging trend, and one that is being driven in large part to offset observed risks of externalizing manufacturing. For our company, owning the facility allows us to quickly advance new updates to our platform from concept to product supply, and rapidly deploy our products. It also enables process robustness through simplified operations while providing immediate operational cost savings.

Minimize supply chain risks

Competition for raw materials will continue and companies will need to think strategically in developing and implementing secondary sourcing plans. Some may need to carry significant inventory to minimize stock-out risk. Developing a business continuity plan early will help companies prepare for risks and enable a quick response to changes in the operating environment.

As the COVID-19 pandemic emerged, our company procured safety stocks of approximately six to nine months, and longer in some cases, for all of our manufacturing materials. In doing so, we did not see a disruption in our manufacturing operations or the ability to supply drugs for our ongoing clinical trials. Developing a robust plan will continue to be critical to any company's collective success — even in a post-pandemic environment.

As the global biomanufacturing market grows, companies will need the right approach to successfully operate new and existing manufacturing sites and deliver value to patients. Designing and establishing robust business processes to remain steadfast, even in the face of challenging and unexpected situations, will be paramount to success.

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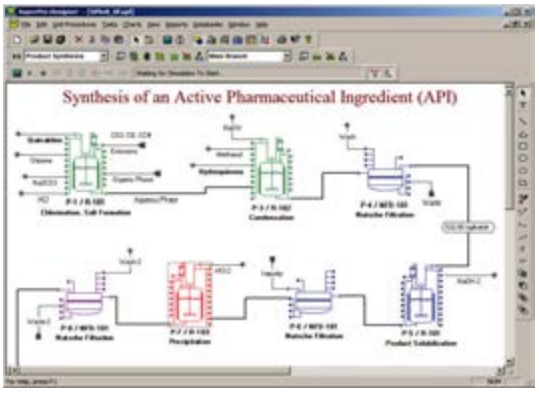

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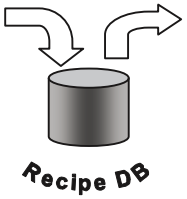

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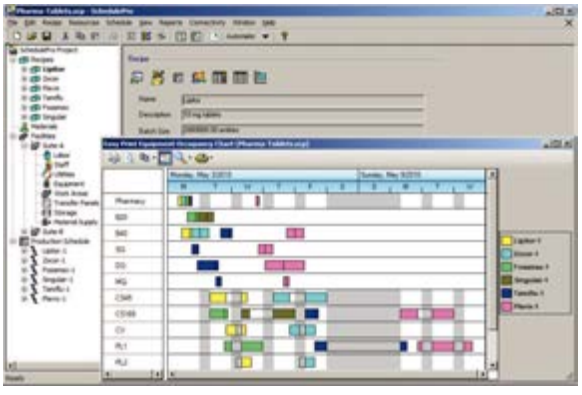

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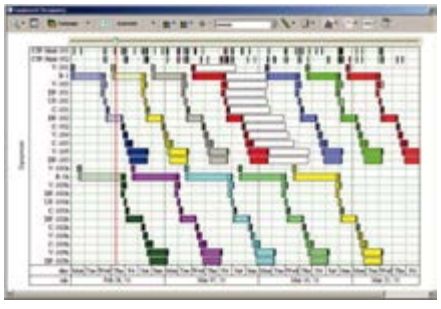

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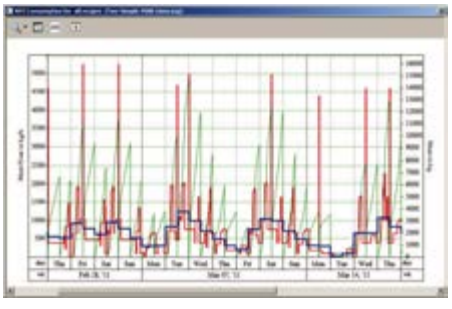
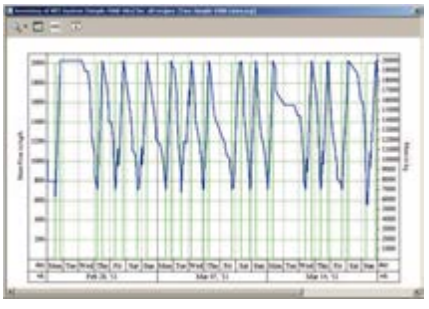


Tracking demand for resources (e.g., labor, materials, utilities, etc.)



Managing inventories for input, intermediate, and output materials

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of integrated biochemical, bio-fuel, fine chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 500 companies and 900 universities around the globe (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor, utilities, and inventories of materials. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size shared utilities, determine equipment requirements, reduce cycle times, and debottleneck facilities.

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Unsung machinery heroes

CNC machining is an underrated aspect of pharma's success story

From incredibly short drug development cycles to cutting-edge mRNA vaccines, the pharma industry's success in combatting COVID-19 bodes well for future medical challenges.

But one underrated aspect of the vaccine success story has been the widespread use of computer numerical control (CNC) machined parts to produce high-end components.

Pharma's growth is expected to continue at a breakneck pace — the worldwide industry has been projected to grow by as much as 160 percent between 2017-2030.

How does CNC machining factor in? Both the production and R&D sides of the pharma industry rely on high-end precision equipment — equipment that can be produced most efficiently via CNC machine tools.

Equipment challenges

Manufacturing equipment for the pharma industry requires two things. First, equipment manufacturers and CNC machine shops need to meet exacting specifications with tight tolerances. Second, they need to conform to various regulatory standards.

To meet these challenges, more and more pharma companies are working directly with CNC manufacturers. This allows companies to get exactly the equipment they need, along with any necessary customization. If needed, CNC manufacturers can even produce custom parts to repair or replace worn parts on older machinery.

Individual tolerances on pharma equipment can also be impressively tight — as little as 0.0002" in some cases. Between the need to conform to industry-wide standards and to produce equipment to incredibly narrow tolerances, pharma equipment manufacturers require the most precise machine tools available.

CNC machine tools are capable of just such precision. CNC manufacturers can produce individual parts or the components necessary to produce pharma lab equipment or production equipment.

For the pharma industry, the latter category is arguably the most important. Pharma production relies on specialized equipment — such as cooling towers, dryers, granulators, tablet presses and coating machines. The industry also uses a range of inspection equipment to ensure quality and consistent production. All of these machines are produced using CNC processes and rely on machine tools.

CNC benefits

Beyond the precision mentioned, CNC provides a number of other benefits to the pharma industry:

- Material flexibility: CNC machining processes work with nearly any material, from advanced plastics to solid metal blocks.
- Design innovation: Integrating CAD/CAM design allows CNC machining companies to work with clients to produce unique, specialized equipment.
- Advanced capabilities: Five-axis machine tools are capable not only of greater precision but also of producing more intricate and complicated parts. This advanced capability becomes especially important as pharma develops new applications and processes.

Using CNC manufacturing techniques allows large and small companies to produce flexible, adaptable, specialized equipment to exacting standards. Since any company can apply for the appropriate ISO certifications to produce pharma equipment, pharma companies can turn to a huge range of producers to meet growing demand.

A future in pharma

CNC technology applies to an ever-increasing number of pharma manufacturing tools. Future applications of CNC technology will open even more possibilities. 3D printing, which uses similar technology to CNC programming, could be used in conjunction with CNC machining to produce advanced equipment more efficiently.

These projections are based only on current CNC capabilities; the advent of entirely new technologies, like artificial intelligence, could dramatically increase both the production abilities and the technical precision of future CNC machinery.

The growing demand for pharma products and the increased budget for R&D will require greater and greater reliance on CNC machining processes to meet the need for precise, accurate and specialized pharma equipment.

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