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Phone: (630) 467-1300 • Fax: (630) 467-1179
www.putmanmedia.com
Subscriptions/Customer Service
(800) 553-8878 or putman@stamats.com

EDITORIAL TEAM

KAREN LANGHAUSER — CHIEF CONTENT DIRECTOR
klanghauser@putman.net

MEAGAN PARRISH — SENIOR EDITOR
mparrish@putman.net

CHRISTOPHER PALAFOX — DIGITAL MANAGING EDITOR
cpalafox@putman.net

KEITH LARSON — VP, CONTENT AND GROUP PUBLISHER
klarson@putman.net

TONY D'AVINO — SALES AND PUBLISHING DIRECTOR
tdavino@putman.net

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Rise of the Underdog

Generic drugs are playing to their strengths and boldly stepping up to challenges

ALTHOUGH DAVID and Goliath has evolved into an iconic underdog story, many scholars argue that David may not have been at a disadvantage after all.

While there are several translations and iterations, the basic gist is this: Goliath, a Philistines warrior, relentlessly challenges the Israelites to send out their champion in a winner-takes-all battle. For 40 days and nights, Goliath yells, but there are no takers (if only he had Twitter). Finally, David, a young shepherd, accepts the challenge. In the end, David, wearing no armor and using only a slingshot, walks away with Goliath's head — giving rise to the most popular tale of a weaker opponent squaring off against a stronger adversary and emerging victorious.

Yet many have called attention to a variety of factors that cast doubt on this seemingly clear-cut case for David as the underdog.

Today's big-ticket fight playing out on the healthcare battlefield is over drug pricing. Generic drugs have stepped up to the challenge, offering a viable solution to combat rising prescription drug costs. Recently, at the Association for Accessible Medicines' (AAM) annual meeting, AAM president, Chip Davis, even referred to generics as the "underdogs" of the drug industry.

Although at times it may seem that way, the "battle" here is not brand versus generics. Questionable patent life extension "shenanigans" are merely one of many challenges the generics industry is up against. The "Goliath" in this tale is an agglomeration of factors, which also include legislative hurdles, market struggles and public perceptions.

Returning to the tale of David vs. Goliath, scientists have theorized that considering Goliath's massive height and size, he suffered from gigantism — an over-production of growth hormones — which often causes blurry vision and even, blindness. Dialogue in the biblical story corroborate the theory that perhaps Goliath was struggling to see his challenger clearly. And then there is the issue of strategy. Goliath had decidedly solid equipment — 125 lbs. of bronze armor and a javelin, spear and sword — but all of this proves to be a hindrance, as David knows how to control the fight's narrative. David rejects the heavy armor and chooses a slingshot — a weapon ideal for a battle fought from a distance.

So, despite being historically heralded as the underdog, David possessed a clear view of the landscape, a strategic position, and a weapon that was better suited for the fight.

Indeed, today's generics now have the benefit of clearer regulatory pathways to approval, especially when it comes to policies aimed at bringing generic competition to complex drugs. Generics, as an industry, also have begun rewriting their narrative, positioning themselves strategically as the most viable answer to the country's number one healthcare problem. And further, their "weapons" rise to this challenge — generic drugs have proven themselves to be effective cures at affordable prices, saving patients and payers nearly $5 billion each week.

And yet, the balance between brand innovation and generic access established by the Hatch-Waxman Act is in serious jeopardy and generics must continue to face off against momentous obstacles.

The jury is still out on David's underdog status. It's entirely possible he *wanted* to be underestimated and that was his greatest advantage. What is clear though is that anyone, underdog or not, fighting what they believe to be the good fight has the potential to rise.

BY KAREN LANGHAUSER, CHIEF CONTENT DIRECTOR
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The Need for Speed: PDA Annual Meeting

THE RATE of change is still increasing at an increasing rate. So, buckle up and get ready to rev your engines or risk being left in the dust. Several speakers at this year's annual meeting for the Parenteral Drug Association — a conference geared towards innovation — harped on this message, urging attendees to make sure they're adopting the right mindset for racing off toward the future.

Innovations aren't all about adopting the latest tech, however. As Steven Spear, a senior lecturer of system dynamics at Massachusetts Institute of Technology, pointed out in his presentation, there's a human element to change.

"What's the most disruptive technology?" he asked the crowd. "People."

That sentiment was echoed in further presentations about navigating executive channels when you have an innovative idea and are facing pushback, and promoting employee resilience to improve operational performance. One of the key takeaways? Don't underestimate the role employees — both incoming and established — play in keeping your companies in the fast lane.

"Build your workforce of the future and build it now," Michele D'Alessandro, vice president and chief information officer of manufacturing IT at Merck & Co., said in her presentation on insights from the manufacturing floor.

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> ROBERT STEWART, PRESIDENT, AMNEAL PHARMACEUTICALS, ADDRESSING THE GENERIC DRUG INDUSTRY AT AAM ACCESS! 2018

Read more in our cover story on page 12.

BETWEEN 2005 AND 2015, 78% OF THE DRUGS ASSOCIATED WITH NEW PATENTS WERE NOT NEW DRUGS COMING ON THE MARKET.

Source: May Your Drug Price Be Ever Green, UC Hastings Research Paper No. 256

FUNNY PHARM

"See what happens? Now we'll have to hire everyone back, just to process all this paperwork."

— Bill Russo

Funny Pharm comics, drawn by professional cartoonist Jerry King, appear on PharmaManufacturing.com. Readers submit suggested captions. Above is February's cartoon and winning caption.

DON'T MISS ONLINE

Building the Workforce of the Future

"At Merck, about 30 percent of our workforce is retirement eligible," Michele D'Alessandro, vice president and chief information officer of manufacturing IT at Merck & Co., said. "If they leave before we have new people in place, without the requisite knowledge transfer, we will not be able to compete as well going forward." This article outlines D'Alessandro's key strategic considerations when shaping an employee base that will keep the company on pace with digital transformations.
bit.ly/PharmWorkforce

Sizing up the Benefits of Sterile Drug Manufacturing Techniques

The need to ensure the safe and sterile transfer of APIs and formulation ingredients during aseptic processing has driven the development of multiple techniques that can be employed in cleanroom environments to minimize the risks from contaminants. This article offers a comparison of several sterile processing techniques, including aseptic isolators, restricted access barrier systems and aseptic Split Butterfly Valve technology.
bit.ly/AsepticOptions

Improving Digital Quality in the Pharmaceutical Industry

It's clear there is no common vision for the role of digital and AI to improve quality within the pharmaceutical industry. Indeed, there is probably a lack of understanding on what it means and what the potential opportunities are. This article describes a vision of how digital could transform quality within the pharmaceutical industries and describes various use cases.
bit.ly/PharmaDigitalQuality

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Industry underdogs look giant challenges in the eye

Generic BUT Mighty

By Karen Langhauser, Chief Content Director

PRESCRIPTION DRUG pricing has arguably become the biggest issue in U.S. healthcare. Indeed, healthcare is an "unbelievably complex subject" and resolving our country's drug pricing problem will be no simple task. When the Trump administration submitted its Fiscal Year 2019 Budget Request to Congress in February, the proposal cited several possible solutions to combat rising drug costs.

One prominent solution highlighted in the proposed budget was generic drugs. The proposal included several provisions designed, in theory, to give the U.S. Food and Drug Administration greater ability to bring generics to market faster.

Health and Human Services Secretary, Alex Azar, has consistently mentioned the administration's strong support for FDA efforts to spur innovation and competition in generic drug markets. During the 2018 Association for Accessible Medicines (AAM) Annual Meeting, this sentiment was echoed by the Honorable Eric Hargan, Deputy Secretary, HHS, when he called generics "vital to the future of our healthcare system."

Generic and biosimilar drugs have rightfully earned their place as part of the solution. In the U.S., generics account for 89 percent of prescriptions dispensed but only 26 percent of total drug costs.[1] Generics have saved the U.S. healthcare system $1.67 trillion in the last decade, generating $253 billion in savings in 2016 alone.[1]

But with far fewer financial and human resources than the branded pharma industry, generics, according to AAM President Chip Davis, are notorious underdogs. Battling public misperceptions, legislative hurdles and anti-competitive actions being taken by brand manufacturers, the generics and biosimilar industries have their work cut out for them in their quest to restore the balance between branded innovation and generic access. But, thoroughly convinced of what Davis refers to as the "unbelievable value proposition" of their products, the generics industry is not going down without a fight.

PERCEPTION IS REALITY

For those connected to the pharmaceutical industry, it may seem difficult to comprehend confusion surrounding the safety and efficacy of generic drugs. Backed by extensive bioequivalence testing, approved generic formulations must provide the same therapeutic effect as branded medicines. The FDA has clear and accessible information on the topic, stating that a generic medicine "works in the same way and provides the same clinical benefit as its brand-name version. In other words, you can take a generic medicine as an equal substitute for its brand-name counterpart."

And yet, numerous public perception studies and literature reviews tell a different story: Many consumers still equate lower price with lower quality. A 2009 U.S. survey[2] found that one-third of patients were uncomfortable with generic substitution to some extent. About 10 percent believed that generic drugs could cause more side effects than brand-name drugs. While more recent surveys have noted a substantial shift towards more patients having positive views of generic drugs (in one study, 88 percent considered generic drugs to be as safe as brand-name counterparts[3]), negative perceptions still linger, especially amongst less educated demographics.

The generics industry's image problem is not helped by frequent news reports of recalls, 483s and import bans connected to manufacturers based in India — the world's largest exporter of generic drugs. In 2015, half of the FDA warning letters were sent to Indian pharma sites, which account for roughly 24 percent of the U.S. generics market.[4] While significant investments in automation, training and regulatory collaboration have resulted in Indian pharma plants receiving less than a third of U.S. FDA warning letters in 2017[5], quality concerns still adversely affect public perception of generic drug safety.

There's also confusion based on superficial details. Trademark laws in the U.S. prohibit a generic medicine from looking exactly like drugs already on the market. Different shapes, coatings or colors can cause confusion and, ultimately, distrust among patients — especially in the case of chronic drug treatment, where patients know and track their meds by appearance.

Whether real or perceived, misconceptions about generic drugs linger, and still present challenges for generics manufacturers.

87% OF PATIENTS SAVE MONEY WHEN SWITCHING TO A GENERIC ALTERNATIVE

MORE THAN HALF OF ALL PATIENTS SWITCHING FROM A BRAND TO A GENERIC MEDICATION REALIZE SAVINGS OF MORE THAN $50

LEGISLATIVE HURDLES

While the generics industry has scored some recent wins on the federal level — the enactment of GDUFA II, which included the reauthorization of the Biosimilar User Fee Act (BsUFA) and the defeat of the FDA's problematic draft drug labeling rule, to name a few — losses on the state level continue to create a challenging backdrop.

At present, 30 states have drafted news laws, dubbed "transparency" legislation, requiring manufacturers to report to the state a variety of information that is thought to justify drug price increases over specified thresholds. For example, in Oregon — the most recent state to adopt a drug transparency law — if a manufacturer wants to increase the price of a drug by 10 percent or more and it's already priced at more than $100 per month, the drugmaker must report costs for R&D, advertising and marketing, as well as profits for the drug, whether generic alternatives are available, and what the drug costs in other countries.

In California, the law applies to drugs worth more than $40 per month, requiring that manufacturers alert state agencies and health insurers 60 days before implementing a price increase of more than 16 percent over a two-year period.

"States are stepping in and attempting to deal with drug costs where they feel federal policies have failed," Davis says.

While only a handful of states have signed these bills into law, according to the National Academy for State Health Policy databases, state legislatures are currently considering 51 bills focused on drug price transparency and 12 focused on price gouging.[6]

AAM has called this type of legislation "well-intentioned but misguided," noting the failure of these policies to account for "the unique challenges facing and biosimilar medicines."[7] In the case of Maryland, the trade group took opposition a step further, requesting a federal injunction on the grounds that the law is unconstitutional.

Maryland's price gouging law — the first of its kind in the U.S. — was signed into law in April 2017 without the blessing of the Maryland governor. Under the Maryland law, drugmakers who increase the cost of an off-patent or generic drug by more than 50 percent in one year can incur a fine of up to $10,000. Maryland governor, Larry Hogan, had expressed concerns regarding the vagueness of terminology used, such as "unconscionable increase" and "excessive," as well at noting possible violations of interstate commerce laws. AAM's injunction request echoed these concerns, claiming that the new law gives Maryland "unprecedented power to regulate interstate commerce," as well as protects high-priced brand name drug companies because it only applies to generic drugs.[8]

In September 2017, a U.S. district judge denied the association's request

for an initial injunction but allowed litigation to move forward on AAM's contention that the law is vague.

Proponents of the Maryland law, however, claim it to be an important step forward in stopping an alarming trend of companies drastically raising the price of older medications. According to transparency law backers, these price hikes often come with no justification in relation to innovation or access.

Policy that doesn't properly address the differences between the generic and branded drug supply chains and markets can threaten the sustainability of a competitive generics market. Basic economic principle dictates that more suppliers of a good creates lower prices for consumers, so, ironically, policy that creates consolidation within the generics industry can also birth a more monopolized environment conducive to the very price gouging these policies seek to eradicate.

SOMETHING HAPPENED ON THE WAY TO MARKET

For generic drugs, last year's record number of FDA approvals (1,027 new generic approvals, five biosimilar approvals) only tells half the story.

According to Davis, one can't measure generic success solely on FDA progress.

"It's a two-step process," Davis says. "While it's true that you can't be on the market without FDA approval, once you are approved, you need sufficient incentives to enter and stay in the market."

So what's holding generics back? In many situations, it's a case of "shenanigans," according to prevailing opinion at the AAM Annual Meeting, as well as FDA Commissioner Scott Gottlieb.

During Gottlieb's meeting with the Federal Trade Commission last fall, he strongly advocated for a balance between rewarding drug innovation and giving patients access to drugs by encouraging competition, pledging that the agency would work to better address unfair practices used by branded manufacturers that forestall generic entry.

In 1984, Congress enacted the Hatch-Waxman Act — a bill commonly considered the cornerstone for competition between brand and generic pharma companies. The act, which established government regulations for generic drugs, has successfully produced a thriving marketplace by balancing innovation in drug development and accelerating the availability of lower cost generic alternatives.

But in an effort to preserve profits on expiring patents, brand manufacturers have begun using tactics that appear to frustrate the intent of the Hatch-Waxman Act, obstructing generic competitors.

One well-known loophole used to delay generic approval is known as "REMS abuse."

The FDA Amendments Act of 2007 gave the agency the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers for certain drugs. REMS programs are designed to help reduce the occurrence and/or severity of certain serious risks, by providing additional safe-use information to patients and providers.

Using REMS as justification, some branded companies have established restricted distribution networks, which means manufacturers of generic and biosimilar drugs cannot get access to product samples they need in order to obtain FDA approval and market entry. In 2017, Gottlieb said the FDA had received more than 150 inquiries to date from generic companies claiming they were unable to access supplies of the reference listed drug to do the testing needed for a generic application.

To address this issue, generic and biosimilar manufacturers began supporting the Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act. Currently pending in Congress, the act allows generics manufacturers who have cleared FDA approval to sue non-cooperative brand manufacturers for access to their drugs in two different scenarios: if the companies fail to reach an agreement on the development of a single, shared REMS system; or if the innovator company fails to provide samples of a drug or biological product within 31 days of request.

There exists strong opposition to the CREATES Act from brand manufacturers, who note both financial and safety concerns. Branded companies claim that requesting companies do not always have adequate safeguards in place to address the unique risks presented by the drug in question, putting both trial subjects and researchers at

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Source: Quintiles IMS, via AAM

risk. Branded companies have also voiced concerns that the CREATES Act will bring about significant and, in their opinion, frivolous litigation costs. Branded companies also claim that being legally obligated to sell samples to generics companies constitutes an obligation to take on the burden of manufacturing enough product for several companies to run multiple studies.

Evergreening (referred to as "patent manipulation" or "life cycle management" depending on which side of the debate you are on) is another well-established strategy used to extend a branded drug's market monopoly. This strategy involves branded manufacturers seeking extra patents on variations of the original drug, such as on new dosages, new combinations or variations, or new forms of release.

The use of evergreening is so prolific that recent research examining FDA records between 2005 and 2015 found that 78 percent of the drugs associated with new patents were not new drugs coming on the market, but rather, existing drugs. Additionally, the research found that of the 100 best-selling drugs, almost 80 percent extended their protection at least once, with almost 50 percent extending protection more than once.[9]

The problem with this, says generic industry proponents, is that companies are obtaining patent protection for changes that are neither innovative or novel, and delaying patient access to more affordable drugs.

"In these cases, you have to ask the most important question: How does this possibly benefit patients?" says Davis.

FIGHTING BACK

For the generics and biosimilar industry, the Goliath-sized battle starts with their own message. In many ways, this is a different approach for an industry not used to advocating to the degree in which the current landscape demands.

"You need to protect your sector like the brand companies have learned to do," said Charlie Cook, famed founder of The Cook Political Report, to a packed room at the AAM Annual Meeting.

Davis echoed that sentiment, advising the industry, "We need to do a better job telling our story."

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AAM is following its own advice. The group rebranded itself last year, shedding the name "Generic Pharmaceutical Association" in favor of "The Association for Accessible Medicines," simultaneously launching a patient-centered multimedia advocacy campaign, and taking an overall more assertive approach to federal and state advocacy.

The generics and biosimilar industries continue to add their voices to the drug cost narrative, hopeful that their efforts to educate and engage both the public and policymakers about generic/biosimilar drugs will help restore the country's balance between generic access and brand-name innovation.

"When we don't engage, we end up living with results rather than delivering them," Davis says.

Among the most important of these results will be greater patient access to affordable, safe and effective medications.

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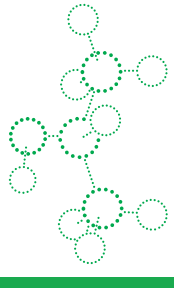

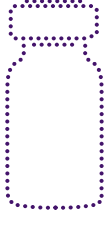

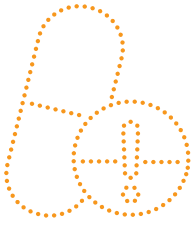

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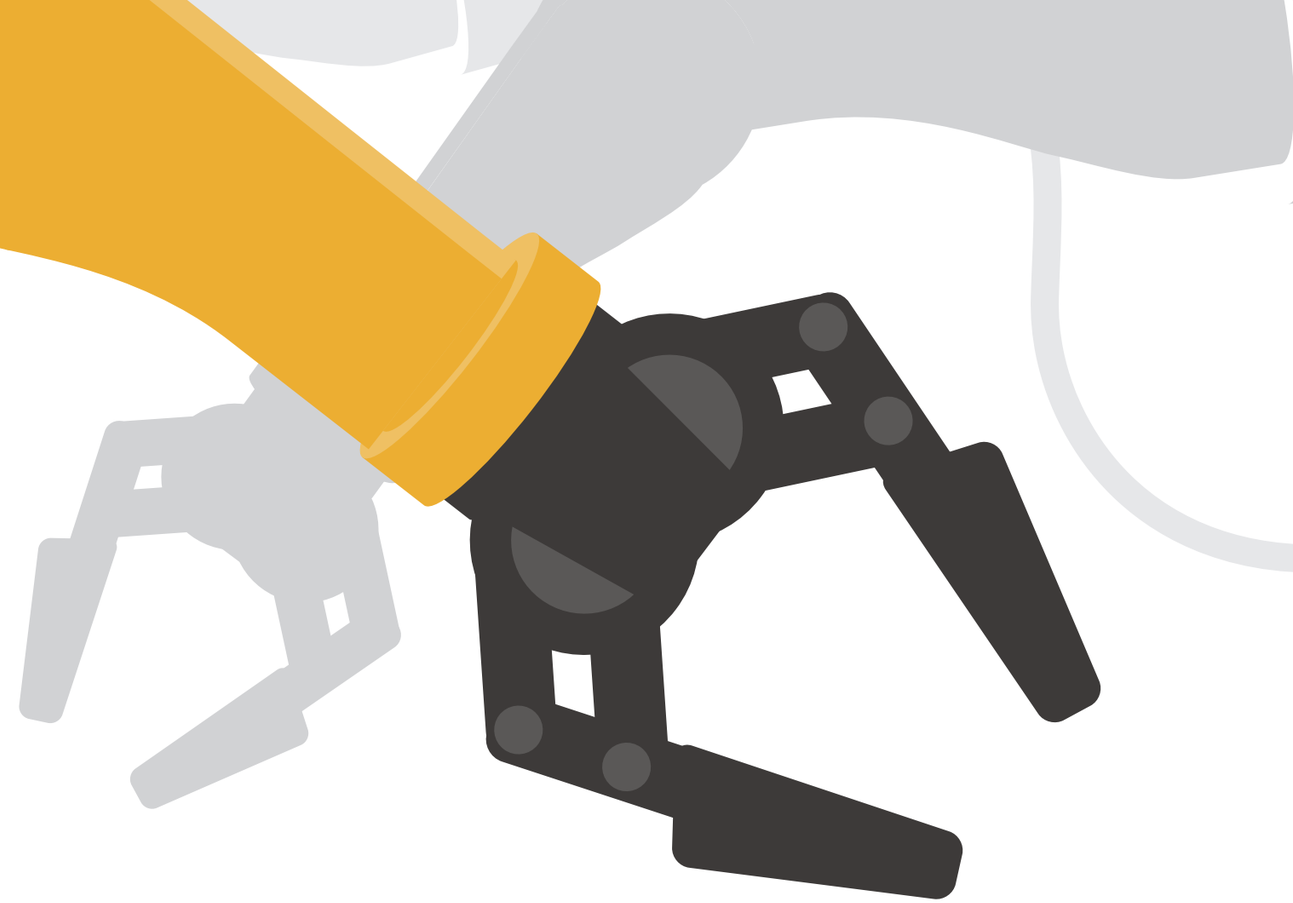


Understanding how Industry 4.0 innovations can transform pharma operations

By John Clemons, Director of Manufacturing IT, and Richard Mondragon, Industry Manager for Life Sciences, MAVERICK Technologies, a Rockwell Automation Company

ANYONE SEARCHING the web for discussions on smart manufacturing and Industry 4.0 will find thousands of articles and countless blog posts on the topic. Many begin with an observation on how consumer tastes are evolving to where shoppers today demand products exactly the way they want.

When Sally Smith, for example, sets out to buy a new car, she doesn't choose one off the dealer's lot. She goes to the company's website, and using the build-it feature, checks all the boxes to design the vehicle with exactly the options she wants. Then the assembly plant builds it just for her.

This works because the whole production system is automated, and creating a one-off car is no trouble at all.

Most smart manufacturing discussions focus on the needs and operations of discrete industries — plants building things, which can be cars, smartphones or electric guitars. This is much different than pharmaceutical manufacturing, for obvious reasons. Mercifully, manufacturers don't receive orders from individual consumers asking for tablets with the exact formulation and dosage wanted. Given these facts, does smart manufacturing even apply to the world of life sciences?

WHAT MAKES MANUFACTURING SMART?

All the elements of smart manufacturing do not apply the same way in every manufacturing environment, but there are some universal underlying concepts. It helps to think about what makes smart manufacturing smart, and how the concepts extend to life sciences.

Smart equipment: Taking the temperature of a product in a reactor can be done manually with a thermometer, or with an electronic instrument equipped with multiple redundant sensors and self-diagnostic capabilities. The latter, used in a smart manufacturing environment, can provide much more data about the product, about itself and about what's happening inside the reactor.

Flexible production equipment: Getting to market quickly with new products combined with easily scalable production are central to smart manufacturing. Products showing promise need fast ramp-up to accommodate demand, so the notion of building a production line to make only one type of product with a fixed production rate is fading fast. Whether building cars or active ingredients, new lines must be configurable and adaptable to a longer list of possible products with quick and easy changeover. Plant facilities are smaller so the equipment footprint needs to be minimized.

Plug-and-play connectivity: Any electronic devices used in a production unit — such as field instruments, valves, PLCs and so on — must be easy to connect and configure, or better yet, self-configuring. Designing more elaborate systems should be easy using a unified programming environment able to communicate with the individual devices. With this type of drag-and-drop programming, it's easy to change the process software.

More sophisticated production equipment: Basic process instruments are giving way to more sophisticated devices. For example, determining the moisture content of granules tumbling in a dryer can be inferred by measuring the humidity of air coming out. But the same measurement can be done more quickly, directly and accurately by using a near-infrared spectrometer, which may also be able to measure and communicate other useful attributes at the same time.

Data gathering, analysis and distribution: The glue that binds smart manufacturing implementations together is data. While the realities of data wrangling are

largely new to many kinds of manufacturers, life science companies are old pros. There is probably no other industry that has been creating and using big data as long. It is available in countless forms in a pharmaceutical manufacturing environment due to the range of regulations watching over every element, from cradle to grave.

The sheer volume of data generated has kept life science companies at the forefront of developing and deploying data retention and distribution methods. There are still technological backwaters to be found in some small areas where manual methods still exist, but these are increasingly rare.

Hardware is a factor in making an environment "smart," but manufacturing data capture, flow and analysis is what ties complex systems together, avoiding isolated intelligence.

COORDINATED, NOT ISOLATED

Looking at these elements together in a group illustrates how different they are. For example, selecting instrumentation is not the same as designing a network, and developing them individually to achieve a common goal requires different approaches. The concepts necessary to make a CIP skid more flexible don't look anything like those needed to reach to the cloud to support better data retrieval. Nonetheless, improvements done in any areas will deliver pockets of better performance to some extent. The real payoff comes with a more coordinated effort to connect the improvements.

Setting up the structure for data exchange is a basic element of smart manufacturing, because getting the right information to the right people at the right time is critical for success. Consequently, the mechanisms to support data flow connect all the elements, making manufacturing into a cohesive process rather than disconnected islands.

Making this work effectively depends on three strategies:

1. Effective process control and instrumentation

Understanding what is going on in a process depends on having the right kinds of instruments in the right places. A temperature sensor mounted in the wrong part of a reactor will not provide the desired information about what is happening in the process. It will create data, but nothing very useful. Processes must be evaluated to ensure the best technologies are being used and applied optimally.

Manufacturing in life sciences evolves slowly due to the conservative nature of the industry and regulatory considerations. Process Analytical Technology (PAT) practices have made improvements easier to implement, but once a process is working and validated, the steps involved with changes are complex. Improvements must promise a significant payoff to be implemented, but they do happen. The industry does evolve, and for the most part it is moving in smart manufacturing directions.

For example, newer production equipment tends to be more modular and built on wheels so it can be moved easily to where it is needed. Connections to join these modules are more standardized in size and position, so assembly of complex trains is easier. Sub-units, such as CIP and SIP skids, need to be easy-to-move and designed to work with a wide variety of process equipment.

Control and automation equipment, including instrumentation, valves and so on, is also more modular to avoid the need for special programming code and awkward connections, both physical and electrical.

One of the biggest developments is the growing use of single-use equipment and processes. Since this approach requires a combination of matching permanent and consumable elements, these are typically handled as preconfigured modular units sold by the equipment vendors. Often this includes predetermined instrumentation placement, and even selection following general GMP and typical process concepts.

In most cases, instrumentation for single-use equipment is adequate for basic needs, but these units tend to be under-instrumented for complex and difficult processes. If deeper process data is required, additions and modifications will likely be needed.

2. Getting data where it's needed

Data in a pharmaceutical manufacturing facility takes many forms. Those responsible for actual production don't necessarily pay attention to results from clinical trials or other phases prior to manufacturing, as they need to zero in on what's happening in the plant, within individual reactors, tablet presses, etc.

Data must make its way from individual instruments and field devices through low-level PLCs to the DCS and process historians. This is a normal situation and happens in any number of process industries. The thing that makes life science environments different is the volume of data and its many forms. The level of detail necessary just to support traceability goes far beyond what most other conventional industries deal with. This kind of data retention and distribution requires sophisticated networking capabilities so all the people that need to see specific bits of information can access the necessary areas.

For example, a lab examines a given batch of product and finds an attribute has drifted out of spec. Lab personnel may then have to dig into the detailed information on the history of all the ingredients, along with all the information related to the specific batch and perhaps any intermediaries produced in the plant. This can involve an enormous amount of data, all of which must be easy to identify and retrieve.

Cloud storage certainly addresses the volume requirements since its capacity is effectively infinite, but it does not ensure easy retrieveability. Good tracking mechanisms must be set up to help guide users to the right data and to keep them from other areas where they have no reason to venture.

3. Understanding what data is saying

As has been said a thousand times: Data is not information. Data becomes information when the right people can apply the right tools to it, extract the secrets buried within, make decisions and take actions based on it. This is a point where many companies fall down. Well-designed networks supporting effective data collection can deliver pages of numbers, but individual users are left to their own devices to make sense of it.

An engineer trying to determine the optimum reaction temperature by comparing temperature curves from multiple batches against critical attributes can end up with a spreadsheet with tens of thousands of cells. With some effort, he or she can probably generate some useful graphs, but it will be tedious and time consuming. Data analytics software is available with capabilities to perform this kind of task far more easily, helping support decision making and pointing out where processes can be improved.

The ability to improve processes, even in a regulated and validated environment, is key to smart manufacturing. All the new features must work together to point at problems and inefficiencies waiting to be corrected, or at least mitigated.

CREATING RETURN ON A SMART MANUFACTURING INVESTMENT

It all sounds good, but what's the financial payoff? How does this help a company improve production and reduce costs? The answers come in many forms and should not be difficult to see. Being able to draw on enough historical batch manufacturing data with sufficient detail to characterize critical product attributes can help optimize a process and increase yields. Equipment utilization can be improved when it's easier to setup and requires less configuration.

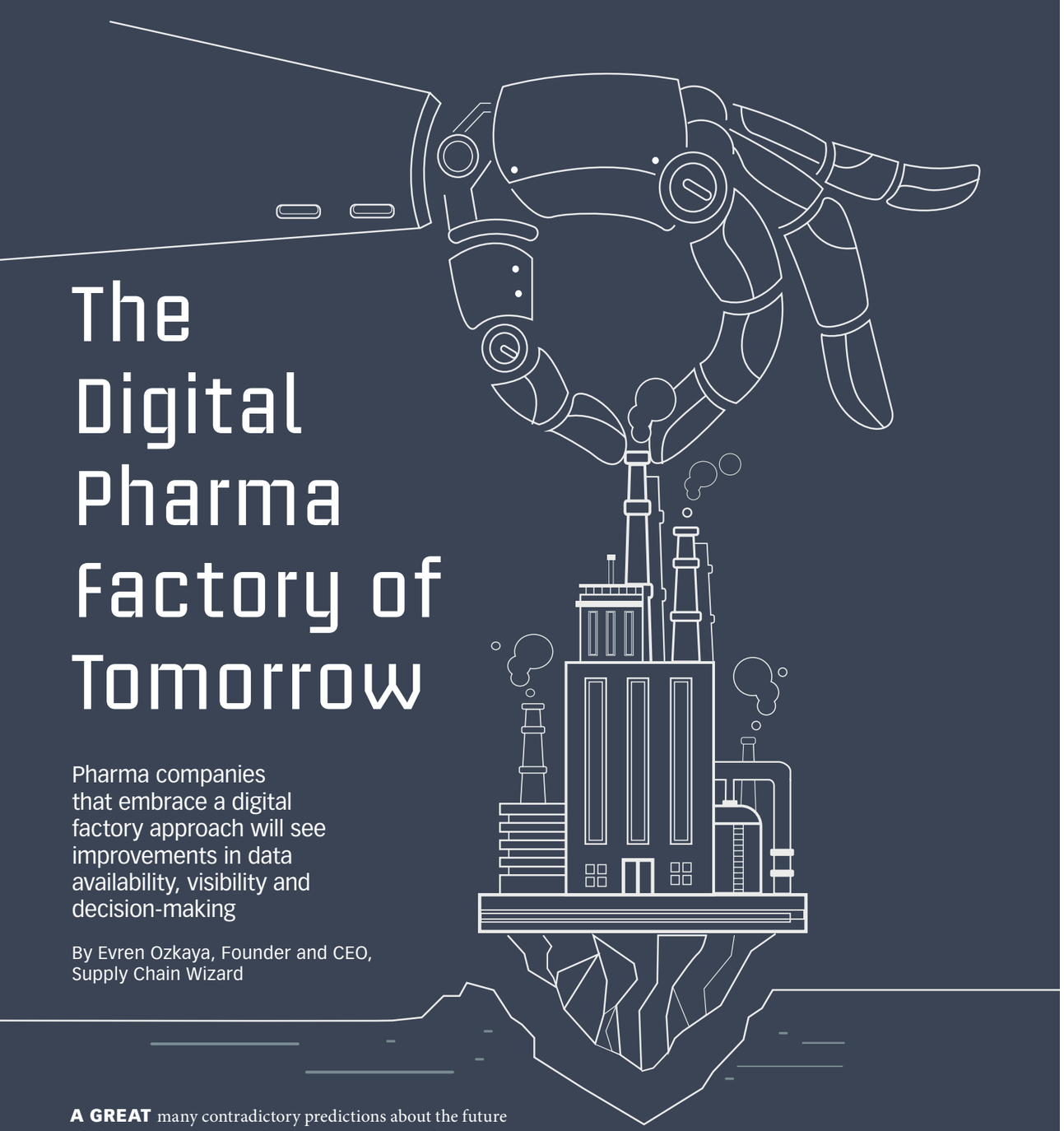
The challenge is creating the systems necessary to make these kinds of changes possible. While the tools to create such systems have gotten better, the systems have grown more complex. Few companies within the world of life sciences have the inclination and internal bandwidth to implement complex networking solutions without engaging external help.

Many companies, such as a DCS vendor, can help with specific parts of the project. But trying to subdivide something this large and complex so individual sections can be given to different service providers ends up creating gaps and awkward hand-off points. Other service providers may have the know-how to create a comprehensive solution, but don't understand the specific needs of life sciences.

A truly helpful service provider needs to bring four attributes to the table:

- Thorough understanding of networking mechanics at all levels, from an individual field device to the c-suite
- Experience within the world of life sciences, including all the intricacies of this heavily regulated business
- Process manufacturing expertise to help unravel the complexities of plant-floor equipment and activities, and
- Business sense to know how all these elements affect the bottom line in the complex world of life sciences.

When all these elements come together in close partnership between the client company and the service provider, smart manufacturing becomes an effective tool to deliver the desired ROI.



The Digital Pharma Factory of Tomorrow

Pharma companies that embrace a digital factory approach will see improvements in data availability, visibility and decision-making

By Evren Ozkaya, Founder and CEO, Supply Chain Wizard

A GREAT many contradictory predictions about the future of pharma manufacturing have been put out into the universe. Some forecasting focuses on looming serialization compliance requirements and their potentially negative impact on packaging and supply chain operations. Others highlight the bright side and focus on the potential impact of emerging technologies, such as the Internet of Things (IoT), artificial intelligence (AI), machine learning (ML) and blockchain.

Of course, the future will vary company to company. Much will depend on the operational strategies chosen — whether these decisions be conscious or subconscious.

DIGITAL VS. TRADITIONAL FACTORY

Let's explore the differing results that may ensue if companies take a digital versus traditional approach to problem solving for various business challenges. We'll call these approaches "Digital Factory" and "Traditional Factory," and imagine five scenarios played out five years into the future, in 2023.

I will highlight the vastly improved results that I predict for those who choose a digital approach. It is my firm belief that with the accelerated rate of change in digital technologies, and the enablement of track and trace infrastructure, a "Digital Factory" approach will result in massive improvements in data availability, visibility and decision-making mechanisms.

Scenario 1: Bidding on a New Business Opportunity

Case Study: A new RFP is received from a major customer looking to select a new CMO partner to produce a high-volume product portfolio, which could increase current demand volume by 30 percent.

Traditional Factory: Management assumes it can fulfill demand without a realistic capacity or cost analysis. Previous RFP submissions are leveraged to benchmark the best price quote, and a final offer is submitted with adjustments to these benchmarks based on management's subjective comments on the negotiation power of the customer and his expectations. If the business is won, the management team struggles to meet demand at all costs.

Digital Factory: Product and volume mix of new business is used in the existing digital capacity model to precisely know the capability to supply, together with implications on internal costs such as additional staff needs, shift restructuring, batch-size driven OEE assumptions, etc. After a realistic cost/supply-side analysis is performed, a reasonable price proposal is estimated based on target gross/net margin assumptions. Multiple scenario analysis is conducted on various volume vs. price points to determine the right negotiation strategy. If the business is won, the management team knows exactly what to do to adjust operational parameters.

Scenario 2: Handling a Crisis — Facing Potential Loss of a Major Customer

Case Study: CMO's largest customer is approached by an alternative supplier and must make a major decision regarding whether or not to transfer 50 percent of its business.

Traditional Factory: Management tries to keep the customer's volume by offering price discounts and other incentives. If the loss is final, management takes reactive actions to introduce severe "across-the-board" cost-cutting to direct and indirect labor and spending to manage this existential threat.

Digital Factory: Using its digital toolkit, management analyzes various "what if?" scenarios of lost volume/revenue in real-time, and quickly ascertains the most suitable strategic operational response. Sales and Operations Planning executives utilize data analytics to oversee the decision making process, calculating outcomes to key metrics such as profitability, and determining the appropriate set of cost-cutting initiatives based on root-cause-analysis and the estimated extent of impact to various business segments.

Scenario 3: Capital Expenditure and Investment Decisions for Capacity Expansion

Case Study: After two years of steady growth in business volume, management decides to expand capacity by building a new facility or expanding current facility capacity.

Traditional Factory: Management decides to buy additional equipment immediately, based on the expectation that the volume growth will sustain and require new capacity in the long term. If the capital expenditure (CAPEX) is limited, management will try to maximize overtime labor, creating a high-cost operational setting to meet the capacity needs.

Digital Factory: Management analyzes the need to add new equipment (or a new site) under various business volume and efficiency scenarios, maximizing the throughput on existing equipment under various shift schedules, and undertakes new CAPEX investment only if truly necessary. Digital analyses highlight bottlenecks on capacity; based on this data, investmest is made in solutions to target these bottlenecks, minimizing capital expenditures while maximizing capacity for a balanced cost/capacity framework.

Scenario 4: Demand/Supply Balancing Using Scheduling

Case Study: High volatility of customer orders requires significant over-time labor cost, so management decides to look at staffing levels and contingent labor strategy.

Traditional Factory: Management hires more labor on a contingent basis and/or asks current staff to work overtime during third shift or weekend shifts. Both scenarios create a high-cost structure, and while the overall utilization stays low, costs go up to manage volatility of customer orders.

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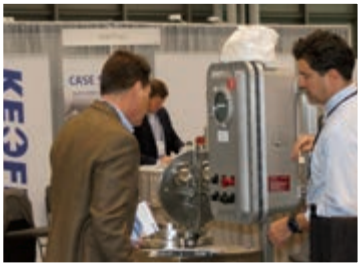
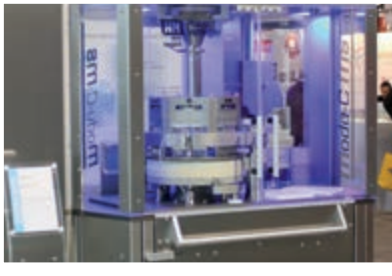

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DIGITAL FACTORY FUTURE

Digital Factory: Management analyzes changes in order of patterns via digital solutions and order/schedule history, and maximizes the utilization of existing staff, while minimizing overtime hours to meet the demand. If customer orders are becoming more volatile, the right balance of staff levels and contingent labor, as well as overtime capacity, is determined based on various scheduling and order scenarios. Digital scheduling solutions help run various simulations to quickly determine the ideal operational parameters.

Scenario 5: Managing a Quality Event or Customer Complaint

Case Study: A complaint is filed from a wholesale customer about a damaged label and a missing unit on a controlled substance product.

Traditional Factory: Management starts an investigation based on this deviation, and makes macro-level decisions to put a hold on all processes that may have led to this adverse event. Due to a slow data collection process across disparate systems, the process can take weeks or months before a root cause can be identified and mitigated.

Digital Factory: Management utilizes all available digital tools to expediently investigate the full history of this specific product down to serial number granularity. All related processes — from manufacturing and packaging to warehousing and shipment — are consolidated within minutes to analyze for non-compliance to business and quality rules and procedures. Any deviations from these standards are analyzed at the serial number and batch level to isolate the root cause. Corrective and preventive actions (CAPAs) can then be implemented based on data-driven insights, further strengthening the processes attributing to this deviation.

A DIGITAL JOURNEY

To achieve long-term success with the digital transformation journey, pharma executives would benefit from a three-phase approach:

Phase 1: Track and Trace/Serialization Compliance and Aftermath

Manufacturers should consider going beyond bare minimum compliance with the U.S. Drug Supply Chain Security Act (DSCSA) and the EU's Falsified Medicines Directive (FMD) of serializing each unit of pharmaceutical prescription drug. It would benefit them to look at the aftermath of packaging operations and supply chain operations efficiency losses, exceptions and related process changes.

Some leading contract manufacturers have already started realizing an increased level of exceptions and operational challenges as they ramp up serialized products, and may want to consider baselining existing "as-is" operations before fully ramping up to a serialized "to-be" operational mode. In other words, there is heightened value in managing Overall Equipment Effectiveness (OEE) metrics very closely. For CMO/CPO businesses, every percentage loss or gain counts, and it would be a competitive advantage to manage operations in a sustainable way.

Phase 2: Digital Transformation

The transformation of factory operations could be simplified into two broad categories. One is the digitalization of any paper-based processes, such as the management of logbooks and batch records, and the leveraging of digital solutions to eliminate cumbersome manual efforts and lack of visibility on any paper archives.

The other is the digitalization of any "spreadsheet-based" tracking sheets, models and processes, such as capacity planning, detailed scheduling and resource management. Handled separately across many versions of spreadsheets, and managed by multiple stakeholders independently, these

processes do not generate the required level of agility, precision and robustness. Additionally, many of these spreadsheet models are often limited by the analytical capabilities of the owner/builder, and are open to human error.

This web of manual processes and spreadsheet models slows down the factory decision making process, making businesses less competitive in an increasingly dynamic marketplace. Creating a roadmap to digitize these recordkeeping/data solutions, as well as dashboard and decision solutions over time, can unlock significant value.

Phase 3: Advanced Analytics and Decision Automation

Once the foundational systems and processes are in place, it's time to move into more sophisticated technologies, such as IoT-based wireless sensors for continuous facility monitoring that can enable business-rule-driven alerts and notifications. Additionally, leveraging the abundance of data and using artificial intelligence to predict downtime (aka preventative maintenance) or detect anomalies in factory processes can offer significantly more value beyond the traditional digital solutions.

Finally, when the digital flow of data and digitized processes are in place, some decision-making processes can be fully automated for minimal human intervention, saving time and adding precision to supply/demand balancing. Additionally, more advanced algorithms using machine learning capabilities can bring hidden insights to the surface, helping executives better understand operational weak spots so they can invest in these bottlenecks to strengthen their operational robustness.

WHICH CHOICE WILL YOU MAKE?

Over the next five years, pharma companies that embrace a digital factory approach are likely to enjoy much greater success than those retaining a traditional approach. Taking this assessment one step further, pharma companies not only should consider digital factory strategies, but also start implementing initial pilot programs to explore the value they can bring to operations. Very often, early proof pilot projects help create momentum and achieve "quick wins" that help fuel future transformation efforts and, possibly, unlock funds to reinvest in long-term business needs.

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The BLOCKCHAIN BOOM

By **Meagan Parrish**, Senior Editor

How the emerging technology could be pharma's savior from costly regulations and counterfeit drugs

THE NEXT revolution in digital technology likely belongs to blockchain. It's already been a game-changing disrupter in the financial industry, where blockchain has allowed for the creation and rise of cryptocurrencies — a digital form of payment that allows users to exchange funds without a central bank.

Now it's knocking on the door of the pharmaceutical world and offering a way to tackle expensive track and trace regulations and fight one of the industry's most pressing issues: counterfeit drugs.

The World Health Organization estimates that fake drugs contribute to the deaths of at least one million people worldwide. The scourge of counterfeit drugs is not only deadly, it erodes people's trust in pharmaceuticals, and, according to the World Customs Organization, costs the industry an estimated $75-$200 billion every year.

To help tighten and secure the pharma supply chain, the U.S. Food and Drug Administration unveiled the Drug Supply Chain Security Act (DSCSA) in 2013, which requires companies to create a system that electronically documents the journey of products from the manufacturing floor to the pharmacy. As the law stands, the deadline to fully implement the new rules is 2023.

The pressure is on companies to adopt some sort of digital solution to track its products — and more eyes are turning to blockchain as a potential answer.

READY FOR TAKEOFF

For years, blockchain was synonymous with bitcoin, the most commonly traded cryptocurrency in the world. Although they are not one and the same, blockchain is the backbone that allows cryptocurrencies like bitcoin to be securely transferred.

Basically, the technology tracks the trading activity of a product in linked "blocks" that are recorded in a chronological "chain." Each party involved in the movement of the product is able to track and view its status, but they can't change any of the history. Once an activity has been recorded, no party can go back and amend it. This transparency promotes trust among the parties involved in the movement of that product.

Because of its ability to track transactions, blockchain is also a natural fit for shoring up supply chain security in the pharma world, which is becoming increasingly complex. In a manufacturing setting, the idea is to use blockchain by assigning goods a unique ID once they are packaged in the plant, then documenting the product as it changes hands with the transportation company, then documenting it again as it is loaded onto a pallet at a shipping dock, etc. until it arrives at its final destination.

Implementing this technology among so many stakeholders will require widespread adoption across the supply chain. And this complexity is partly why blockchain technology is yet to be fully developed. Yet, blockchain has successfully worked as the backbone for bitcoin for nine years, and industry experts estimate that in just a few years, blockchain will be the go-to supply chain solution.

Mark Toohey, CEO of TBSx3, a startup focused on implementing blockchain-based solutions in several industries, compared the progress of the technology to the development of aviation.

"Bitcoin proved that humans were capable of flight," he says. "Now we're in the biplane era and we're going to keep building it until we're in the jet age. There are many layers and tools to build, but it will happen."

The company, which stands for "to be sure, times three" has developed a solution that will provide three layers of protection for products that are changing hands: encryption of a unique ID for each package; an integrated and fully auditable track and trace solution that monitors movement of the goods from the production line to the store shelf; and blockchain's "no double spend" feature which means each ID is unique. The standard business practice for counterfeiters is to copy a unique item (including any associated ID) a vast number of times. If the copied ID can only be validly sold once then the copies are rendered commercially useless. This, according to Toohey, will help destroy the market for fake drugs.

$176 billion

The business value of blockchain technology by 2025, according to predictions from Gartner Research. The firm estimates that number will rise to $3.1 trillion another five years later.

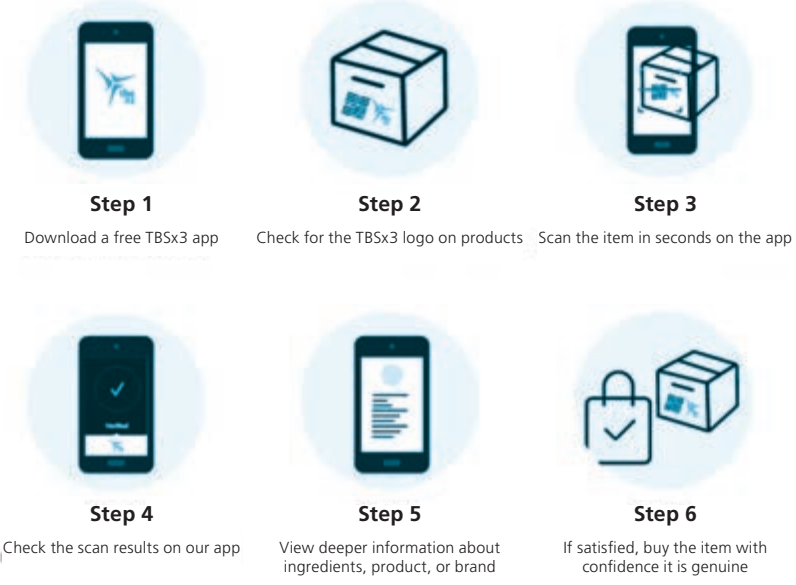
Toohey says he became interested in the promise of the technology after surviving cancer with the help of chemotherapy and finding out that there have been instances, even in U.S. hospitals, when patients have received fake chemo.

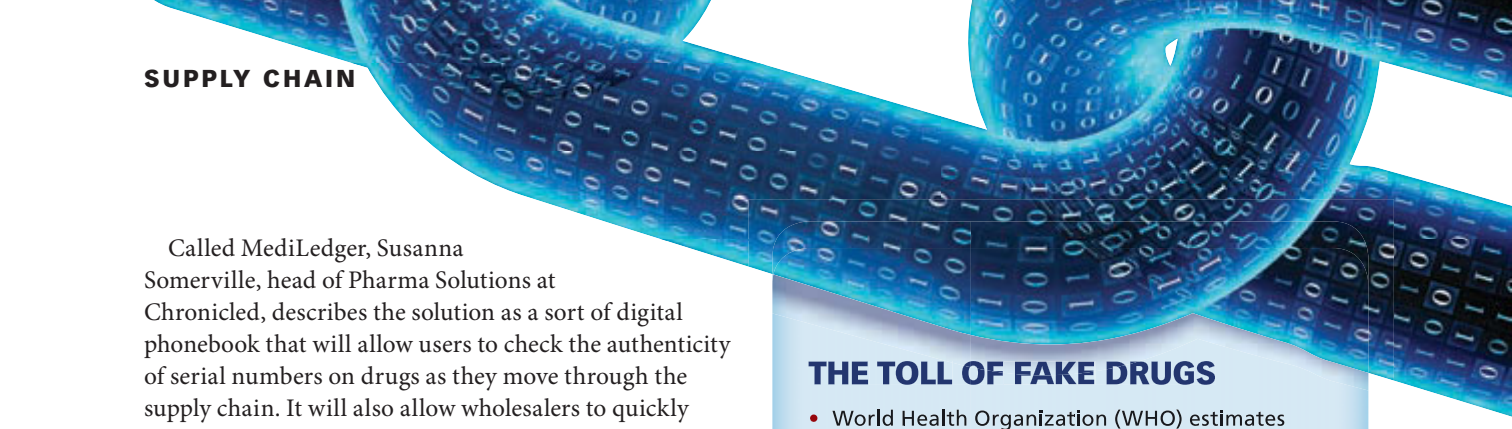
"[That] was a turning point," he explains. "I said, 'Now I know that's what I want to do with the rest of my working career.'"

TBSx3 is ready to roll out its blockchain solution, and the company has already scored major partnerships with several key participants such as some of the biggest names in the freight shipping business, including DB Schenker and DP World Australia. TBSx3 is also in the process of working with several major pharmaceutical companies to set up trials. Toohey says he envisions that in the pharma industry, drugmakers will be the "brand owners" or investors into the solution, but then it will be available as a free application for mobile and other devices and easily implemented throughout the supply chain.

THE REGULATORY FIX

While TBSx3 is working on a major rollout, a California-based startup called Chronicled plans to begin trialing a new solution this summer that it calls a "baby-step" toward fully integrated blockchain.





Called MediLedger, Susanna Somerville, head of Pharma Solutions at Chronicled, describes the solution as a sort of digital phonebook that will allow users to check the authenticity of serial numbers on drugs as they move through the supply chain. It will also allow wholesalers to quickly communicate with the manufacturer on all returned product intended for resale, and allow them to comply with the law while delivering sub-second verification.

Chronicled hopes MediLedger could evolve into a network-wide solution that will be adopted by major service providers like SAP and integrated into their current track and trace platforms. Although there are multiple solutions utilizing blockchain in development — and some companies are even inventing their own solutions to stay compliant with DSCSA — Somerville says she predicts that the market will eventually migrate to well-established and tested networks.

As for the next step and implementing blockchain through the supply chain? Somerville says that will largely depend on pharma companies themselves. If more drugmakers jump into the race to create blockchain solutions, the technology will advance more quickly. But if many aim to put off DSCSA compliance until the last minute (or bank on the rules being delayed to an even later date), blockchain will sputter. The quicker this solution is developed, the faster companies will realize the further benefits of blockchain.

MORE IN STORE

For the pharmaceutical industry, the potential benefits of blockchain go beyond track and trace.

"Imagine that we have a system that is focused on recoding the shipment of drugs," Somerville says, explaining a next-use example for blockchain. "Now take that and then automate the payments."

At many pharma companies, there are entire departments dedicated to investigating payments in the supply chain. Once developed, blockchain technology could create an automated payment and verified receipt every time the product changes ownership.

"That is the real pot of gold waiting for these companies," Somerville says. "They are doing it for compliance but there are huge financial savings as well."

Chronicled is also looking at ways blockchain could be used for raw material verification, temperature monitoring with deliveries and managing chain-of-custody for centralized medicines.

Others have envisioned a way to use blockchain to streamline the clinical trials process to more quickly move compounds through the pipeline. Toohey says a recall function could also be added to their solution to help locate and round up medications.

THE TOLL OF FAKE DRUGS

- World Health Organization (WHO) estimates that **10 percent** of all drugs in low to middle income countries are substandard or counterfeit.
- Worldwide sales of fake pharmaceuticals reached **$1.1 trillion** in 2015, according to the Fraser Institute.
- The WHO estimates that at least **100,000 people** are killed from fake or substandard drugs each year in Africa alone. The market for fake drugs was formerly dominated by medicines that people were often too embarrassed to ask physicians for, such as sleep aids or erectile dysfunction drugs. Now, **more than half** of the market is flooded with fake drugs for dangerous diseases such as malaria, tuberculosis and cancer.

ROADBLOCKS TO BLOCKCHAIN

Although the technology has the hype and momentum to realize its full potential, there are several key hurdles to widespread adoption. Firstly, the development hasn't been lightning fast.

"It's a slow technology, but it is meticulous and rock-solid accurate," Toohey says.

It's also possible that if pharma companies have already invested in a solution for DSCSA compliance, they won't want to make a costly leap onto the blockchain bandwagon. Uncertainty with the new technology could also prompt companies to wait and see until there's widespread adoption and a clearer return on investment.

But as with any new technology, putting short-term cost considerations ahead of long-term investment opportunities could mean that your company misses out on the best solution. In the same way smart phones quickly progressed from a novel curiosity to transforming our daily lives, the pace of further developments with blockchain is likely to increase once it hits the big stage in the pharma world.

"It does take time for a new technology to get that deep traction, but once it does, there are winners and losers," Toohey says. "Those who delay are often left out. The same will happen in manufacturing and finance as this new technology embeds itself."

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THE RISE OF HAZARD CHEMISTRY IN Drug Development

The growing demand for hazardous chemistry brings new risks that require both chemistry and engineering expertise

By Paul Moscrop, Process Engineering Manager, Sterling Pharma Solutions

AS NEW chemical entities (NCEs) with greater molecular complexity enter drug development pipelines, the demand for hazardous chemistry techniques is growing.

Hazardous chemistry can provide access to synthetic routes for active pharmaceutical ingredients (APIs) which overall involve fewer process stages. These alternative routes of synthesis are not always considered during the earlier phases of development due to the risks involved. But, ultimately, these routes allow API manufacturers, with the right experience, to develop more direct and cost-effective processes that will produce higher yields.

However, it's vital that manufacturers carefully assess the risks involved and have the necessary expertise and experience to review and manage the potential impacts of operating any process involving hazardous chemistry.

THE REQUIREMENT FOR HAZARD EVALUATION

As the risks associated with hazardous chemistry become more prevalent, higher standards are being enforced through stringent regulations to protect both the health of those working in the industry and the reputations of developers.

In Europe, Directive 2012/18 — Major Accident Hazards (MAHs) (Seveso III directive) requires that operators should take measures to prevent major accidents, and to limit their consequences for people and the environment. The demonstration is achieved by risk-based assessment.

Assessing the level of risk associated with a manufacturing process requires the identification and understanding of the inherent reaction hazards unique

to that process. It's recommended that every process manufactured, whether it's at a 20-liter scale or 10,000-liter, undergoes a rigorous hazard evaluation. This will involve the process being subjected to a full run-through a reaction calorimeter (RC1) to identify heat outputs from reactions and quantify gas generation. At key points in the process, samples of reaction mixtures should be taken and assessed through differential scanning calorimetry (DSC). This screens for thermal activity and decomposition temperatures. In some situations, accelerated rate calorimetry (ARC) can also be performed. This process can identify thermal onset temperatures for runaway reactions and any associated pressure rises. A vent sizing package (VSP) can then be used to assess gas generating reactions and emergency venting requirements during scale-up.

Powder handling is one of the most significant causes of incidents within the process industries. As the most common compounds used in the manufacture of APIs are powders, it's vital to identify hazards associated with their use. Tests including minimum ignition energy (MIE) identification, 20-liter sphere tests for dust explosion classification and electrostatic charge relaxation identification are recommended.

THE ROLE OF THE PROCESS ENGINEER

Process engineers will use the information provided by hazard evaluations to inform the design of a manufacturing plant. Reaction heat outputs will help define the control strategy for material additions, reactor cooling systems and gas evolution quantities, while rates will help define the size of vents and exhaust gas abatement systems. Insight into both the equipment used and instrument failure modes will help establish the emergency cooling and venting requirements necessary to prevent loss of containment, while also confirming emergency shutdown systems and response procedures.

Collaborations with development chemists and multidisciplinary process review meetings will help ensure that all details are shared and incorporated into the design. For example, does the reaction mixture thicken? Do solids suspend easily? If agitation is stopped, does the mixture layer? While a process engineer may propose changes to minimize the consequences of any hazards, this should not be done in isolation and additional testing and approval by a chemist should be sought.

Hazard identification and risk assessment can be conducted on the final design of a manufacturing plant using fixed process and piping and instrumentation diagrams (P&IDs). Should an MAH be identified, these will need to undergo more in-depth risk assessments that are proportional to the severity of the hazard. This may include a layer of protection analysis (LOPA) or a quantified risk assessment (QRA). If protective instrumentation is a requirement, the safety integrity level (SIL) will also need to be defined.

The need to consider alternative chemistry is one of the most common outcomes following a safety review. This could involve a change in solvent system, a different order of operation or alternative reagents. Again, collaboration is vital here and chemists and engineers must work together to minimize or eliminate all hazards.

If MAHs are identified, manufactures will be required to submit a report to the competent authorities in their region. This must provide an overview of the hazards, anticipated consequences/impact and control measures put in place. The overall premise is to demonstrate that the process is safe to operate within the nationally recognized levels. If the MAH is associated with the use of specific materials, manufacturers will be required to justify that the chemical route is the most appropriate for the desired molecular transformation. This needs to take into consideration the environmental impact, as well as the hazardous nature of the materials. The results of the hazard

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evaluations can be used in these circumstances to demonstrate why alternative routes present greater hazards.

PRACTICAL APPLICATION OF HAZARDOUS CHEMISTRY

Testing of all processes prior to manufacture will serve to significantly reduce the potential for hazards. Identifying any hazards in the clinical trial phase of development can bring considerable efficiencies to overall development programs. After validation, the chemistry is generally fixed, which makes it more challenging for manufacturers to make changes. Early identification can influence the choice of reagent to eliminate or, at the very least, minimize the consequences.

FINAL THOUGHTS

For today's API manufacturers, it is a prerequisite of development programs to achieve complex synthesis in high yields with high selectivity in as few steps as possible. In many instances, hazardous chemistry will be the most cost-effective and environmentally responsible pathway to the development of a new molecule.

The potential MAH consequences associated with traditional batch processes has necessitated that evaluations are undertaken to establish a complete understanding of all hazards associated with a process and put in place measures to eliminate or minimize the impact of these on both human safety and the environment. This is fundamental in justifying the safety of a manufacturing plant to regulators.

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A welcome step from the industry are the advances that are being made in continuous manufacturing of pharmaceuticals. It's anticipated that these may be used to reduce the risks associated with the processing of hazardous materials. The continuous flow of materials can significantly reduce the inventory during critical steps. As a result, it can limit the consequences should the control systems allow the materials to reach onset temperatures. It is important to note that investment in these processes may still be in the same region as implementing a new batch reactor. However, in addition to risk reduction, cost saving benefits can be achieved further down the line through reduced requirements for system maintenance and supporting regulatory audits.

Hazard evaluation is fundamental to API development and strategic planning from the initial stages of a development program is critical in achieving successful outcomes. An approach that combines both chemistry and engineering expertise is essential. With careful planning, manufacturers can ensure the right teams are put in place to ensure the precise and efficient control of process conditions.

The Evolution of Quality

Good quality doesn't have to mean higher costs — in fact, it often means lower recall and warranty costs

By Adriana Aragon, Evgeniya Makarova, Alessandro Faure Ragani, and Paul Rutten, McKinsey & Co.*

DISASTER HAS a way of concentrating the mind. Massive recalls and lawsuits — over luxury cars, over-the-counter medicines, medical devices, or mobile-phone batteries — become almost totemic reminders of what a lapse in quality can mean. And for manufacturers everywhere, simultaneous increases in supply-chain complexity and media reach mean that the aftershock of a quality lapse is likely to be much larger than in the past.

But despite their impact, these events are only part of the story. As important as it is to prevent rare disasters, focusing too closely on them can distort an organization's understanding of what quality really means. Fundamentally, quality is about meeting or exceeding customer expectations: every day, every shipment, year after year. That's where the true value is, measured not only in higher revenues from greater customer satisfaction but also in higher operational efficiency and effectiveness due to increases in productivity and innovation — and even employee engagement.

Yet, organizations face constraints. Rising margin pressures, particularly in consumer-oriented industries, such as fast-moving consumer goods and medical products, limit how much companies can spend on quality practices. Organizations therefore cannot just be good at quality — they need to be smart about it as well.

To achieve the right balance, organizations must learn to think about quality systematically. At the very earliest stage of quality awareness, organizations start to hear the voice of the customer more clearly, while stabilizing their operating systems and promoting greater transparency about quality problems. As these practices take hold, the next stage of maturity centers on strengthening cross-functional accountability and collaboration for quality — such as with new performance standards — so that

quality standards inform the design of products and the management of supply contracts.

At the third stage, quality informs much of the organization's decision making, embedding itself so deeply that it becomes a part of the culture and essential to the company's value proposition. Finally, among a small group of the very highest performers, quality becomes the basis for their reputation. These exceptional organizations expand their perspectives on quality to address customer problems in ways that push their businesses into new areas, building on behavioral research and process analytics to develop deeper solutions and customer relationships.

Achieving these outcomes requires investment. But the good news is that the organizations whose quality practices are the most sophisticated are not necessarily the ones that spend the most on quality. Instead, these leaders prioritize, so that what they spend on quality is highly effective. At each stage of maturity, the advantages build: from essentially nonexistent to basic, and then to average, advanced, and finally, industry-leading.

For example, a multinational industrial manufacturer that was at an early stage reduced its "cost of nonquality" — such as for warranty claims, waste and rework — by about 30 percent. A midlevel biopharma facility reduced product deviations by more than 50 percent and waste by three-quarters, while also freeing more than 25 percent of the employees allocated to catching quality issues for reallocation to other activities. And, pushing still further, in pharmaceuticals, the top producer's costs were a mere one-fourteenth of the median level. At every stage, therefore, companies across industries are achieving

Exhibit 1

MATURITY STAGE	OPERATING SYSTEM	QUALITY SYSTEM	CULTURE
Starting	Inconsistent manufacturing performance	Reactive, minimal compliance	Limited attention to quality
Typical evolution trigger: opportunity to reduce quality costs (eg, financial, reputational), compliance requirements			
1. Basic	Progress toward repeatable, standardized manufacturing	Development of individual quality processes Establishing basic compliance standards Launch of separate quality function	Increased transparency about product quality Focus on improving compliance
Trigger: opportunity for quality to generate positive value and reduce quality risk exposures and failure costs			
2. Stronger	Robust manufacturing, some identification of improvement opportunities	Quality systems established in all functions Greater cross-functional accountability Active problem solving for quality	Quality as customer value Focus on reducing cost of quality
Trigger: opportunity for quality to rise from "table stakes" to substantial part of value proposition			
3. Embedded	Continuous improvement cycle for manufacturing	Quality and customer satisfaction drive product design and solutions, strategic decisions	Quality is the way the company works Focus on anticipating customer needs and continuous improvement
Trigger: opportunity to redefine what quality means			
4. Standard-setting	Adoption of advanced manufacturing and control technologies, and advanced analytics to inform new product and process design	Quality draws on unique capabilities and innovation, becomes a source of insight and an enabler of breakthrough products	Quality is one of the most valuable company attributes, focus is on developing solutions beyond the company's traditional boundaries

higher quality at competitive cost, building capabilities that prepare them for further stages of quality evolution.

QUALITY MATURITY: FOUR EVOLUTION STAGES

In assessing an organization's quality practices, we focus on three foundational elements of quality.

The first is the operating system — the manufacturing processes for an automaker or the service operations for a bank, for example — gauging how well it can contribute to quality. Second is the quality system itself, including enterprise-level capabilities such as measuring quality output, or incorporating quality standards into the design of products and processes. The third element is the cultural dimension of quality — the way employees think about how they contribute to and ensure product quality.

How an organization performs in these three areas determines its stage of maturity (Exhibit 1). Although the boundaries between the different stages are not precise, each nevertheless correlates with a few important characteristics.

From the experiences of organizations that are investing in quality, a few broad lessons stand out. Most important is that investments can pay off at every possible starting point — from stage zero, when a company has very few quality capabilities, to stage four, when it is among the standard-setting organizations that are redefining what quality can mean.

A further, related lesson is that the impact from investing in quality tends to increase with the organization's quality maturity. That's partly because of scale: As maturity increases, quality involves more and more of the organization. And it's also because quality increasingly informs strategy so that its effects are broader and longer lasting.

The final lesson, however, is that progress at each stage is neither smooth nor automatic — nor even necessary, depending on the organization. Instead, progress comes from triggers that share certain features, even if the details are inevitably specific to the organization.

Stage 1: Building the basics of customer focus, transparency, and stability

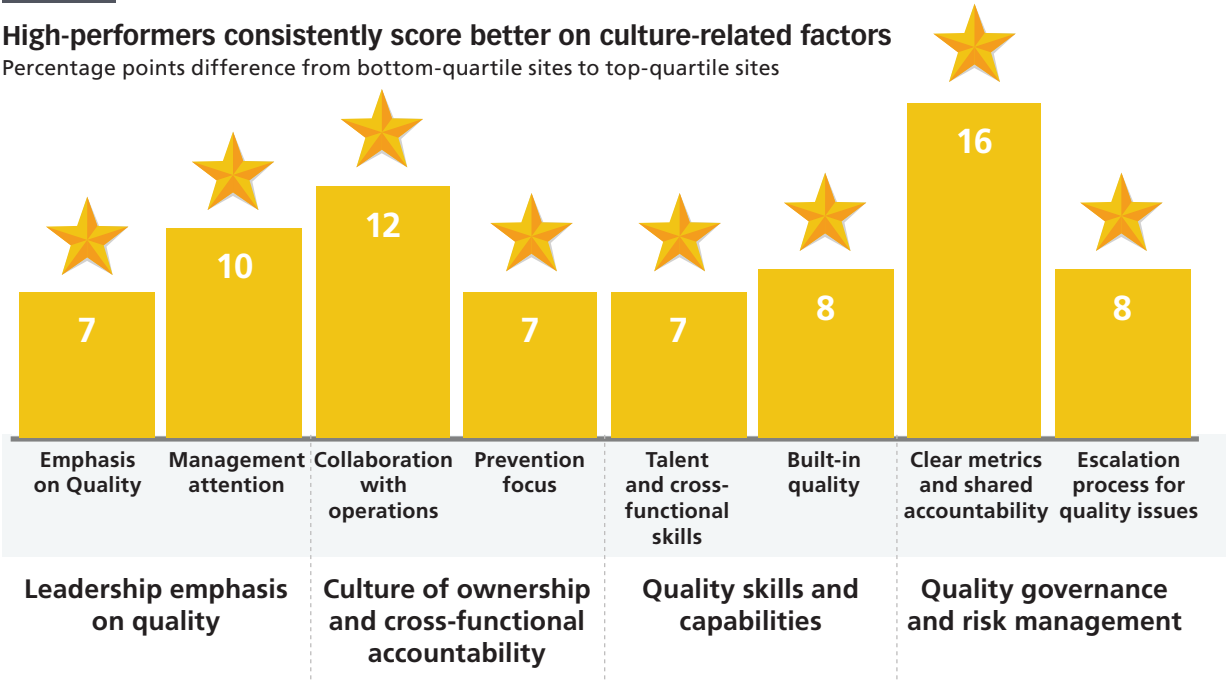
The first trigger typically occurs when the organization recognizes that simply reacting to quality problems is no longer tenable. Often, it simply costs too much — in recalls, warranty expenses, and lost reputation. And it's a lesson that applies equally to a start-up that has focused mainly on growth, a state-owned enterprise protected from market demands, and a company in a high-demand industry.

That was the case for one multinational manufacturer, a giant in a sector that was suddenly becoming far more competitive as global demand plummeted. The leaders recognized that stronger quality would be essential to survive the industry's downturn. Current quality levels

Exhibit 2

High-performers consistently score better on culture-related factors

Percentage points difference from bottom-quartile sites to top-quartile sites



were not meeting customer expectations. At one facility alone, more than a tenth of production was defective in some way. Deliveries were often late — so often that it damaged the company's credibility with crucial customer segments. And claims costs were far too high.

The underlying issue, the company found, was a mentality in which quality was the responsibility of the quality organization — and no one else.

To change this long-standing mindset, the company started by listening to customers more carefully. Partly as a result, it changed its most important performance metric from "units produced" to "quality units produced," which dramatically increased transparency on quality throughout the enterprise. Equally importantly, a new quality council — headed by a C-suite executive and including business-unit and functional heads — set the tone with a weekly one-hour meeting focused on quality improvement. Following basic lean-management structures, a cascade of similar meetings carried the quality message through each level of the company, from plant general managers down to a daily ten-minute quality huddle for each operating shift.

The results? A more stable manufacturing environment in which customer complaints and quality-related costs both fell by more than one-quarter.

Stage 2: Strengthening the culture for tighter collaboration

Once an organization's quality becomes more transparent and stable, new opportunities often arise to increase quality's value and decrease its cost. Our latest research confirms that higher-performing manufacturing sites score better on culture-related factors than their peers (Exhibit 2). Accordingly, at this stage, the goal becomes to enable greater collaboration across the entire organization so that quality becomes embedded in the culture. That collaboration extends outside the organization as well, to include stakeholders, such as partners and regulators.

Two pharmaceutical manufacturers illustrate how this stage evolves. One, a generics maker, was facing compliance issues and needed to establish better quality operations on the factory floor. The other, one of the world's largest branded manufacturers, reexamined its compliance practices for ways to improve its quality outcomes and risk profile — while reducing costs.

To reinforce the cross-functional nature of quality, both companies expanded their use of broad performance measures, such as error-free or right-the-first-time (RFT) production and on-time, in-full delivery. In team huddles throughout their production sites, the companies focused on daily tracking and discussion of the new indicators. In addition, tying these shared metrics to annual bonuses increased everyone's attention to quality — not just within their particular functional or operational units but also across organizational boundaries.

As these new practices took hold, productivity at the generics manufacturer's sites increased by more than 15 percent, while its end-to-end RFT percentage rose from 83 percent to more than 92 percent. Individual sites started passing regulatory inspections more confidently and without any noted compliance issues or regulatory observations. For the branded pharmaco, the changes reduced both the number of quality incidents and its cost of poor quality, improving its risk profile with no added investment in IT, capital or other resources.

Stage 3: Turning quality into the core value proposition

The third transition deepens the quality culture until it becomes the company's core value proposition. In effect, quality is no longer mainly a question of bottom-line savings but of top-line revenue generation. Tactically, this stage requires renewed investment in human and digital capabilities so that the company can consolidate all available customer data — from every internal touchpoint, and from external sources as well — to identify new openings.

A global logistics company's transformation of its quality approach illustrates the level of commitment required. Previously, the company's focus had been on fast delivery, a goal it had largely achieved. But customers increasingly looked at other factors, such as accuracy in predicted delivery times; speed was not necessarily helpful if a delivery arrived before the customer was ready to receive it. Moreover, the rise of a digital economy meant that deliveries were becoming far more complex: fewer large deliveries to warehouses and retail stores, and more very small deliveries to residential addresses.

The new world demanded not just high quality but also quality leadership. The entire organization, from the executive suite to the drivers, immersed itself in capability-building sessions to understand the competitive reasons for higher quality and the implications for day-to-day work. Deeper problem-solving methodologies allowed people to identify new ways to serve customers. And new technologies crunched route data to enable wholesale restructuring of delivery practices that minimized the chance for errors. The result was a major increase in customer satisfaction and renewed growth.

Stage 4: Setting a new standard with the latest analytics and technologies

The final stage applies the wider range of measurement

and analytic technologies to develop solutions that push well beyond the organization's traditional business in predicting emergent customer needs — sometimes before the customers themselves are aware of them. One early example comes from commercial-vehicle manufacturing. Historically, most of the value a manufacturer could earn came from the initial sale. But one large commercial-vehicle maker now monitors more than 100 separate performance indicators in its vehicles. Based on advanced component-wear modeling, the company can deploy repair personnel to its customers before any failure occurs, increasing vehicles' utilization rates while reducing maintenance costs — and rapidly growing the service side of the business.

At the level of individual manufacturing sites, advanced analytics are increasing output and decreasing waste. A passenger-vehicle maker has cut downtime for its manufacturing equipment from days to hours. In chemicals, sophisticated modeling of energy inputs and demands can reduce energy usage by five percent or more. An appliance manufacturer used a cloud database to store several sources of information (for example, repair-technician notes, warranty-claims data, call-center records, product information, and manufacturing data), for which predictive analysis gave it early warnings of issues and allowed it to improve its design processes for both future and current products. And in less than two years, a biopharma site more than doubled its yield and RFT levels — with minimum additional process investments — by deploying advanced analytics to better understand important process variables and improve process specifications.

Not every organization needs to achieve the highest level of quality maturity — and certainly not all in one go. But all organizations should recognize that when a trigger looms, an investment in quality capabilities can often open new opportunities for competitive advantage.

Adriana Aragon is an analyst in McKinsey's North American Knowledge Center, Evgeniya Makarova is a partner in the Chicago office, Alessandro Faure Ragani is a senior expert in the Milan office, and Paul Rutten is a partner in the Amsterdam office. *The authors wish to thank Phil Duncan and Anil Sikka for their contributions to this article.*

Avoiding a Mix-Up

The latest tech and tricks for purchasing the best mixing equipment

Meagan Parrish, Senior Editor

THE TECHNOLOGY for manufacturing-grade mixers hasn't changed much over the years.

In fact, when manufacturers are shopping for mixers, they often want to purchase an exact replica of a mixer they invested in years ago. This is often the case because changes to equipment could require that the manufacturer go through the process of revalidating it through the U.S. Food and Drug Administration.

"Changes to mixing equipment are typically slow, mostly with minor changes to make improvements," explains David Dickey, founder of MixTech, an engineering consulting firm specializing in mixing technology and equipment. "Many equipment requests from pharmaceutical companies are for identical equipment purchased previously."

But this doesn't mean that vendors are not working to continuously update and tweak the design of mixers to meet the evolving needs of manufacturers. And when a company is shelling out a large investment for a new piece of equipment that will hopefully stand the test of time, it's important to get the purchase right.

Here are some of the issues facing pharma manufacturers looking to purchase a mixer and how vendors are rising to the challenge.

The Silverson Ultra Sanitary In-Line is a multipurpose high shear mixer designed for clean-in-place and sterilize-in-place operation.

COMMON PROBLEMS

Most pharmaceutical manufacturers face similar issues when shopping for mixers, according to Rick Earley, the national sales manager for Admix. These "process pain points" include:

- Long batch times
- The ergonomics and safety of batch operators dumping bags or pails of ingredients into tanks from elevated platforms
- Consistently producing uniform batches with 100 percent utilization of all functional ingredients
- Dusting
- Air entrainment

To help combat those common challenges, Earley recommends that companies look for mixers that reduce batch times by completing all ingredient wetting and dispersing in-line "without the need to wait on conventional tank mixers to complete the job." Unlike open-air tanks, in-line mixing also ensures that no air is added to the product and eliminates the dusting problems that arise when products are dumped into the tank.

Mixers with floor-level hoppers are also safer to use because operators won't have to climb stairs with heavy bags and pails.

Earley notes that Admix's Fastfeed powder induction and dispersion unit includes all of these features and that the system "inducts, wets and disperses from the hopper at the same rate each time, virtually eliminating batch-to-batch inconsistencies that result when operators dump powders into tanks at different rates."

THE NEED FOR CLEAN

Sanitation is, of course, always of the upmost importance to drugmakers, and sanitation regulations are only getting stricter.

"To respond to legislative and customer requirements, the pharmaceutical industry is having to demand ever-increasing standards of sanitary construction in mixing and processing equipment," explains Matt Smith, a sales director at Silverson Machines.

MANUFACTURERS SHOULD WORK CLOSELY WITH MIXER VENDORS TO MAKE SURE THEY'RE ON THE SAME PAGE.

Smith recommends that manufacturers look for ultra-sanitary mixing equipment specifically aimed at the pharmaceutical and biotechnology industries.

"Certified by regulatory standards such as 3-A and cGMP, all of Silverson's mixers can be designed or modified for ultra-sanitary applications, including mixing sterile ingredients, vaccines, ointments, suspensions and injectables," Smith says. "The mixers feature a minimized number of product contact parts, crevice-free construction and sanitary shaft sealing."

The all stainless steel 40-gallon Ross PowerMix Planetary Disperser with touchscreen PLC recipe controls is ideal for mixing high-solids, high-viscosity applications.

GOOD COMMUNICATION

Although mixing technology has mostly stayed consistent in recent years, the needs of manufacturers are becoming increasingly complicated. This complexity makes it all the more important to make sure your company is clearly communicating its unique process specifications to vendors.

"This has to do with new kinds of medicines that are being developed, such as liquids, ointments and gels," says Dickey. "New products and processes often have different physical properties or different mixing requirements. These days, typical problems involve non-Newtonian viscosity, powder and liquid addition, powder blending of minor ingredients, and scaling up production."

Dickey recommends that manufacturers work meticulously to make sure they are on the same page with mixer vendors to ensure they get equipment fit for their needs. Mixer vendors also often have the right expertise to help manufacturers solve processing issues with their products.

Christine Banaszek, a sales manager at Charles Ross & Son Company, also stresses the importance of communication.

In an attempt to achieve greater batch-to-batch consistency, more customers are standardizing on PLC-based recipe controls, says Banaszek. This level of automation often necessitates extensive integration, and the best way to ensure a smooth start-up upon delivery of your mixer is to source the control system direct from the equipment manufacturer.

"At Ross, we have our own controls division, which oversees the engineering, design and production of all control systems for Ross mixers and blenders."

Ultimately, Banaszek says that Ross works closely with the end-user to "identify opportunities to streamline the mixer/control design, ensure compliance to code requirements, and to provide smooth, intuitive interfacing with upstream/downstream equipment and mobile devices."

"No one size fits all," Banaszek says, explaining that Ross offers customized programming and HMI configuration, as well as software and data logging options.


ANDA Tips From the FDA

How the generic drug industry can submit more complete applications

BY RENU LAL, PHARM.D., CDER'S SMALL BUSINESS AND INDUSTRY ASSISTANCE (SBIA), DIVISION OF DRUG INFORMATION (DDI), AND LISA BERCU, REGULATORY COUNSEL, CDER'S OFFICE OF GENERIC DRUGS (OGD)

AS PART of the FDA's efforts to encourage generic competition through implementation of the Drug Competition Action Plan, the agency is working to make the Abbreviated New Drug Application (ANDA) submission and assessment process more efficient and effective.

Earlier this year, the Office of Generic Drugs (OGD), in coordination with the Office of Pharmaceutical Quality (OPQ) and other offices in the FDA's Center for Drug Evaluation and Research (CDER), released a new guidance for industry and established more streamlined internal practices to help reduce the number of review cycles for ANDA approval. The draft guidance, *Good ANDA Submission Practices*, and the *Manual of Policies and Procedures (MAPP) 5241.3, Good ANDA Assessment Practices*, apply insights gained through the implementation of the first five years of the Generic Drug User Fee Amendments (GDUFA) program to improve application quality and increase assessment efficiency.

Until now, approximately half of all ANDAs with GDUFA review goals required at least three review cycles to reach approval or tentative approval. The reauthorization of GDUFA (GDUFA II) improves the predictability and transparency of ANDA assessments by fostering the development of high-quality submissions and resubmissions. These enhancements should help to get generic products to market more quickly.

GOOD ANDA SUBMISSION PRACTICES GUIDANCE

The draft guidance describes common deficiencies in ANDA submissions that may lead to delays in approval. It also provides recommendations to applicants on how to avoid these deficiencies. Key recommendations include:

Patent and Exclusivity

- Submit timely written documentation of the sending and receipt of notice of a paragraph IV certification.
- Monitor the Orange Book and quickly address newly listed patents, revised patents, and exclusivities.
- Submit required notification of commercial marketing to FDA within the designated 30-day time frame.

Labeling

- Ensure that draft versions of container labels and carton labeling "reflect the content, as well as an accurate representation of the layout, text size and style, color, and other formatting factors that will be used with the [final printed labeling]."
- Ensure the color and/or format of container labels and carton labeling are adequately different from other pending/approved products in applicant's product line.

Product Quality

- Submit complete drug substance information in a drug master file (DMF) or in Module 3.2.S.2.2, including characterization of the API with all potential impurities and justification for their specification.
- Follow FDA and ICH guidances to provide a complete product quality evaluation.
- Provide complete manufacturing facility information in Form FDA 356h.
- Communicate with contract manufacturing facilities about CGMP-related roles and changes in inspection status.

Bioequivalence

- Provide complete bioanalytical study reports and methodology validation data, plus accurate and complete information for model summary tables.
- If there is a deviation from a relevant product-specific guidance, provide the justification and supportive data.

THE FDA IS WORKING TO MAKE THE ANDA SUBMISSION AND ASSESSMENT PROCESS MORE EFFICIENT AND EFFECTIVE

MAPP — GOOD ANDA ASSESSMENT PRACTICES

The FDA has also established a MAPP with good ANDA assessment practices for OGD and OPQ to improve internal operations. The MAPP clarifies the responsibilities of primary assessors, secondary assessors, and division directors, which will reduce duplicative/unnecessary work.

We expect these changes will allow the FDA to focus more attention on novel or challenging scientific and policy issues associated with generic drug products. The FDA remains committed to increasing competition in the prescription drug marketplace, and facilitating the entry of safe, effective and affordable generic drugs.

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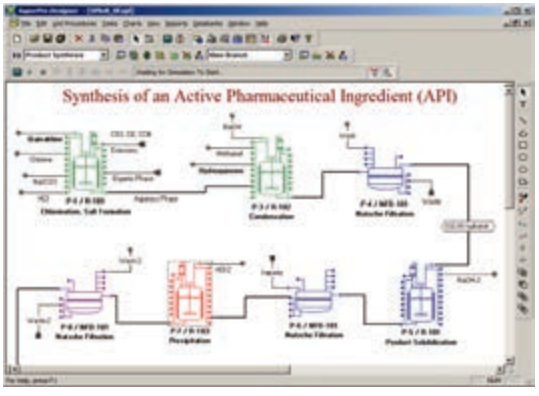

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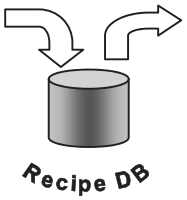

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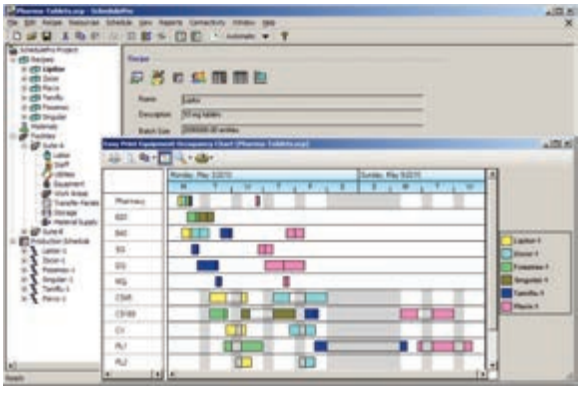

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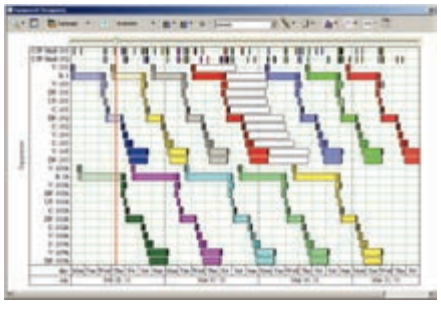
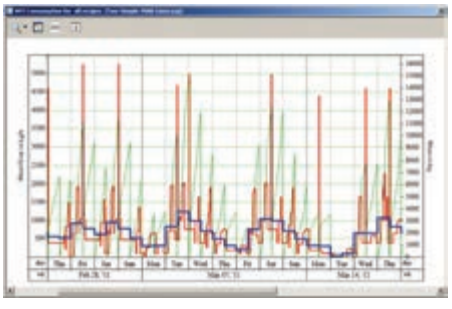
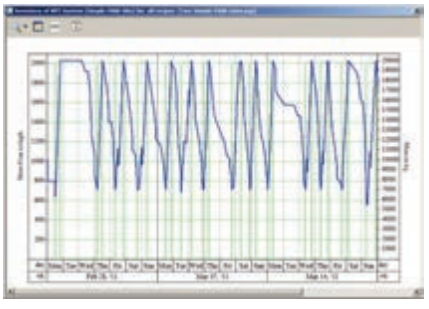


Easy production tracking, conflict resolution and rescheduling



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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SALES

JIM BAKER — **PUBLISHER**
jbaker@putman.net

GREG ZAMIN — **REGIONAL SALES MANAGER**
gzamin@putman.net

JIM RICHARDSON — **SALES DIRECTOR**
jrichardson@putman.net

POLLY DICKSON — **CLASSIFIED SALES/ ACCOUNT MANAGER**
pdickson@putman.net

HILLARY FREELEY — **VP, ADVANCED DIGITAL SOLUTIONS**
hfreeley@putman.net

CARMELA KAPPEL — **ADVERTISING COORDINATOR**
ckappel@putman.net

JILL KALETHA — **REPRINT MARKETING MANAGER, FOSTER REPRINTS**
jillk@fosterprinting.com
866-879-9144 ext. 194

PRODUCTION

RITA FITZGERALD — **PRODUCTION MANAGER**
rfitzgerald@putman.net
630-467-1300, ext. 468

ADMINISTRATION

CARMELA KAPPEL — **ASSISTANT TO THE PUBLISHER**
ckappel@putman.net
630-467-1300, ext. 314

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Automation Keeps Pace

Automation technology required to support new approaches is just as important as the inherent attractiveness of the manufacturing process itself

BY PETER ZORNIO, CHIEF TECHNOLOGY OFFICER, EMERSON AUTOMATION SOLUTIONS

MANUFACTURING METHODS in the life sciences industry are in the midst of dramatic transformation. Single-use manufacturing technologies, after a long "trial" period, have come into their own as a mainstream option, offering a combination of lower capital costs, flexibility, and reduced cleaning. Continuous manufacturing is also gaining traction, including recent regulatory approvals, with those looking for the highest production capacity with the smallest footprint.

When discussing new techniques, the conversation tends to focus primarily around the production process, physical equipment, operational characteristics and relative costs. However, the automation technology required to support these new approaches is just as important as the inherent attractiveness of the manufacturing process itself. If suitable measurement products, control software and hardware, and record collection capabilities are not available from dependable suppliers in an easy-to-deploy manner, then the promise of these new methods can't be broadly recognized. We can't fully realize the benefits of breakthrough technologies if highly customized and expensive automation is required to make it a reality.

One example is sensing technology for single-use applications. In traditional manufacturing, sensors and their electronics are permanently installed in fixed equipment and periodically calibrated for compliance. When sensors for single-use manufacturing contact the process, they must be disposable if the single-use promise of reduced cleaning is to be recognized. This has driven the development of new, sterile sensor components that measure different properties and are plugged into placeholders in the throwaway bag, and then connected to fixed, reusable electronics with all the calibration, self-diagnostics and electronics of traditional, permanently mounted instruments.

When control equipment (DCS, PLC, etc.) and software are considered, we find the current generation has mostly been designed for the traditional stainless steel vessel batch manufacturing processes. Integrated, sophisticated batch software has been developed that works well in these configurations, but it expects equipment configurations to be fixed or to have a limited number of permutations directly incorporated in the software.

Conversely, when we look at single-use, one major envisioned advantage is modularity and the ability to "mix and match" potentially mobile unit operations to meet a specific manufacturing process. Once this "new" process is established, it is highly desirable to have it appear as an integrated process to the operations staff, similar to permanent construction. This challenges the control system software that runs these processes. Automation companies have responded by developing modular controllers that can be attached to each of these unit operations and provide autonomous control and visualization. When networked together, these controllers automatically merge configurations into a single integrated database to provide a unified operational view.

WE CAN'T FULLY REALIZE THE BENEFITS OF TECHNOLOGIES IF EXPENSIVE AUTOMATION **IS REQUIRED TO MAKE THEM REALITY.**

Continuous manufacturing brings the opposite challenge: Unit operations are highly coupled to each other, and control functions must consider the impact an action in one operation will potentially have on another. During product transitions, control software must "learn" and react to the changed control characteristics of the specific process associated with the specific product. In fact, unless the right control software technology is available, the process can't be reliably operated as envisioned — much like it took new computer-driven flight control technology to enable a new generation of more maneuverable jet fighter aircraft with highly coupled control surfaces.

New manufacturing techniques are enabling more cost-effective personalized meds, lower capital cost facilities, faster time to market and increased production. The development of the automation technologies that enable them to do so are vitally important to their broad-scale deployment. The future continues to be bright for pharma businesses not just because the processes and process technologies are being revolutionized, but also because the underlying control solutions are keeping pace with these advances.

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