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Race to the biosimilar space

Pharma navigates unfriendly terrain to reach the next frontier in affordable drugs

By Karen Langhauser, Chief Content Director

We live in a truly exciting time for the advancement of biologic treatments.

Biologics are the fastest growing class of therapeutic compounds in the United States, giving chase to the traditional small molecule model that defined the pharmaceutical industry for more than a century. While small molecule drugs still dominate the U.S. market in terms of quantity, the current pharma pipeline contains over a thousand innovative new biologic hopefuls — including a range of novel scientific approaches such as cell and gene therapies, RNA therapeutics and conjugated monoclonal antibodies.

But being at the top means you have to defend your throne. As the industry's biggest biologics begin to fall from the patent cliff, lack of affordability and access is creating a huge opportunity for the next frontier in medicines: Biosimilars.

Per U.S. regulations, a biosimilar is highly similar to and has no clinically meaningful differences in safety, purity and potency from an existing U.S. Food and Drug Administration-approved reference product — with prices that can be almost 50 percent lower than branded biologics.

However, the key word in the biosimilar discussion is still "opportunity." Ask some drug manufactures what it's like launching a biosimilar onto the U.S. market, and they might equate it with trying to undertake a mission to the moon. Of the 18 FDA-approved biosimilars, only seven are actually available commercially in the U.S.

The addressable biosimilar medicines market, 2016–2020*

Potential savings in USA
$250 billion

Potential combined savings of France, Germany, Italy, Spain and the UK
$50 billion

*Addressable market is calculated based on projected growth of originator market without biosimilar entry.

COURTESY OF THE INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION (IGBA)

Why the failure to launch? In a sector where we should be making giant leaps, we instead appear to be inching forward at a less-than-desirable pace for those waiting for affordable options to pricey biologics, as well as for manufacturers who want to capitalize on a sizeable market opportunity.

What can be done to ensure that drugmakers and patients alike in the U.S. don't lose the biosimilar space race?

POTENTIAL BACKED BY FACT

It's well known that Europe is far ahead of the U.S. when it comes to biosimilar approvals and commercialization. The European Medicines Agency (EMA) approved its first biosimilar in 2006 and to date, 58 biosimilars have been approved in the EU, across eight therapeutic classes.

Commercialization varies by individual country, but biosimilar penetration is healthy and it is not uncommon to see 30-40 biosimilars on the market in an EU country.

By contrast, the U.S. did not see its first biosimilar approval until 2015. But in this scenario, being behind offers a distinct advantage — there is already 10-plus years of market data available, courtesy of Europe.

"Biosimilars have already proven themselves in Europe," says Edric Engert, founder of Abraxeolus Consulting and former head of the Biosimilars Unit for Teva. "There are over 700 million patient days in Europe [As of March 2018]. Biosimilars have been incredibly efficacious and incredibly safe," he contends.

The financial benefits are there as well: Biosimilar medicines have already delivered savings of around $1.6 billion in the five largest EU markets alone.[1]

Despite this preponderance of evidence, biosimilars still haven't entirely taken root in the U.S., and

experts say there are several explanations for the slow uptake.

BIOSIMILAR EXPLORATION

The term that both clarifies and confuses when it comes to biosimilars is “interchangeability.”

In the U.S., there are two distinct regulatory pathways for biosimilar approval: A drug candidate can simply be approved as a biosimilar, or the drug manufacturer can add an additional step and apply to have its biosimilar approved as interchangeable — but this distinction requires additional data and carries a separate application fee. To date, none of the biosimilars on the U.S. market carry interchangeable designations. And this likely won’t change, says Christine Simmon, executive director of the Biosimilars Council, a division of the Association for Accessible Medicines (AAM).

“When every dollar counts, interchangeability designation doesn’t confer any additional product attributes or quality standards,” she says.

Not considering all biosimilars to be interchangeable is creating an acceptance barrier, even though interchangeability itself would not have an effect on the majority of biosimilars.

The FDA is clear about not endorsing interchangeability for “regular” biosimilars.

“When FDA carries out a scientific review of a proposed biosimilar, the evaluation does not include a determination of whether the biosimilar is interchangeable with the reference product and whether the biosimilar can be substituted for the reference product at the pharmacy,” the agency has stated.

This distinction is not just made by the FDA — it is written into the Biologics Price Competition and Innovation Act (BPCIA) — which further complicates the issue by making interchangeability not just a regulatory term, but a legal one.

Globally, while the EMA does not directly make decisions regarding interchangeability, biologics are considered interchangeable upon approval. Per the EMA, “biosimilars approved through EMA can be used as safely and effectively in all their approved indications as other biological medicines.”

“Unfortunately, the U.S. is the only country that has a separate designation of interchangeability for an approved biologic. It’s another barrier that serves to foster the impression that an interchangeable biosimilar is somehow superior in quality to a non-interchangeable biologic,” says Simmon.

Exploring biosimilars in the U.S. was important enough to warrant the creation of a separate advocacy group. Formed in 2015, the Biosimilars Council came to fruition to address a void identified by many AAM member companies that were involved in the biosimilar space. The only U.S. trade association dedicated solely to the education and policy advocacy of biosimilars, the council has successfully extended AAM’s reach into the newest frontier in affordable treatments.

SYSTEMIC CHALLENGES

In addition to the confusion surrounding interchangeability, biosimilar manufacturers are up against several systematic commercialization challenges in the U.S. These barriers, says Simmon, "have forced the U.S. biosimilars industry into a perpetual state of infancy."

"Each challenge needs to be identified as either systemic to the industry or unique to the product, therapeutic area or originator being challenged. It's important to make this distinction since the approaches and solutions will vary across these two spaces," says Engert.

Trust and confidence

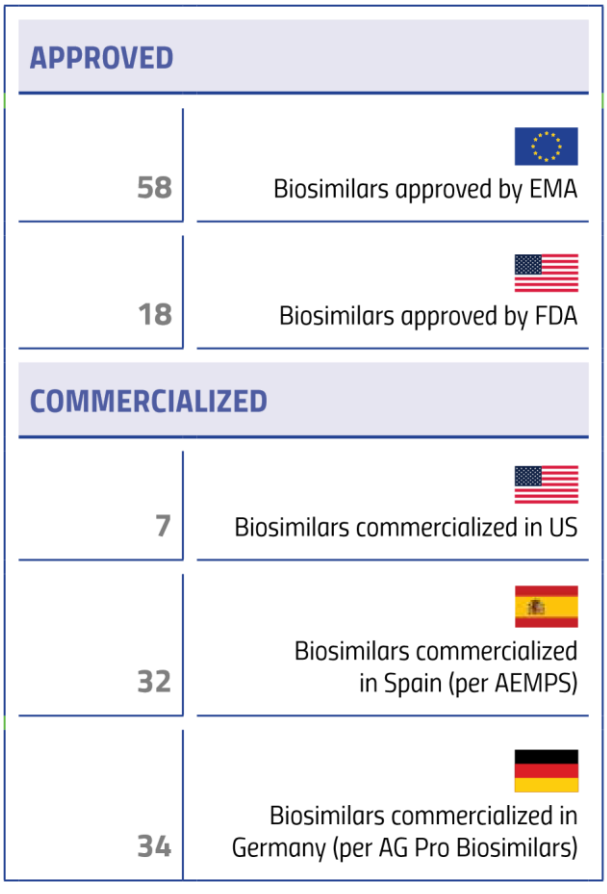
Although generics and biosimilars are often lumped into the same category, the two are in very different evolutionary stages when it comes to public, physician, and payer confidence. Currently, generics account for close to 90 percent of prescriptions dispensed in the U.S. and have over a 30-year history of safety and efficacy with U.S. patients. By and large, the public trusts generic drugs.

Generics have the benefit of automatic substitution at the pharmacy level. Because of this, the rate at which generics penetrate the market after initial introduction is very high — with generics typically capturing most of the market (in some cases up to 90 percent) within a few months of entry. By contrast, the first product approved by the FDA as a biosimilar, Zarxio (Sandoz), became available on the U.S. market in September 2015 and ended the year with a 2 percent market share. Over three years postlaunch, Zarxio has about 35 percent share of the U.S. filgrastim market.[2]

Part of the onus falls on regulators. In March, the FDA updated its 2017 draft guidance on biologic drug naming — stating that the agency will continue to assign four-letter suffixes to newly approved innovator biologics, biosimilars or interchangeable biosimilars. The agency justified this as a matter of pharmacovigilance: In case of an adverse event, wanting the ability to determine whether its source is the biosimilar or biologic. Health Canada recently decided that they will proceed without the addition of a product-specific suffix, making the U.S. the outlier in this construct as nearly every other highly regulated pharma market does not require a suffix for the purposes of biological product naming. This includes the World Health Organization (WHO) which generally decides the naming construct for pharmaceutical product classes.

> Even if you get FDA approval and wind your way through the pa
> thicket and emerge from the other side, it won't matter if you can'
> market share.
>
> — Christine Simmon

Approved biosimilars versus commercialized biosimilars



The biosimilar industry and insurers balked at this, arguing that the FDA should assign a biosimilar the same nonproprietary name as the reference product on which it was based in order to facilitate substitution by providers and pharmacists. This "meaningless addition," says Simmon "creates a distrust and apprehension that is completely unfounded and not based on science."

"The naming guidance is an artificial construct that the U.S. has created and is supported primarily by companies that are trying to avoid competition and protect monopoly prices," says Simmon.

Unfortunately, a large part of the blame for eroding confidence comes from within the industry itself.

Pfizer is the leading biosimilars company worldwide by revenue, and the U.S. leader in biosimilar approvals with five, three of which are commercialized. According to Pfizer's vice president, Corporate Affairs Lead, I&I and Biosimilars, Juliana M. Reed, one reason why the uptake of biosimilars in the U.S. has been limited relates to "dissemination of false and misleading information by biologic manufacturers that creates doubt and confusion among stakeholders about the safety and efficacy of biosimilars."

The drugmaker has been bullish in its efforts to challenge practices that block competition and biosimilar options for patients. In August of last year, Pfizer submitted a citizen petition to the FDA, requesting that the agency issues guidance to ensure truthful and non-misleading communications are made concerning the safety and effectiveness of biosimilars. Pfizer also cited multiple, specific examples of misleading communication from brand manufacturers.

The petition was later supported by advocacy groups, such as the Biosimilar Council, as well as other drugmakers, including Novartis.

"Every time you spread misinformation around biosimilars, not only are you undermining the FDA approval, you are sowing the seed of doubt for providers and patients who are still learning about biosimilars," says Simmon.

According to Pfizer, more still needs to be done. "We believe proactive measures must be taken to incentivize and cultivate a biosimilars market that prioritizes patient access," says Reed.

IP battles and litigation Innovation in biologics does not come cheaply. The innovator biologic process is characterized by long discovery and development times, costly failures and high clinical trial investments. Biologics, which generally rely on multiple patents, have a standard 20-year patent protection granted from the U.S. Patent and Trademark Office, beginning from the time the patent is filed (typically prior to clinical trials). Given that development is often a lengthy process, occurring after the patent clock starts ticking, the BPCIA provides innovator biologic sponsors with a generous 12 years of market exclusivity following the biologic's FDA market approval.

However, branded pharma companies often seek to protect their products from competition by filing dozens (and in the case of AbbVie, hundreds) of follow-on patents, creating a "patent thicket" around their branded product. Challenging patents can be extremely expensive — even if some of the patents are eventually found to be invalid or unenforceable, patent litigation can be a huge deterrent for potential biosimilar competitors.

"This is a big problem because a biosimilar competitor has to have the financial wherewithal to challenge these patents in order to reach the market," says Simmon.

The risk involved when there is patent litigation is often too great for biosimilar manufacturers to take on.

"Even if you think you can prove some of the follow-on patents to be invalid and others you can circumvent, are you really going to launch at risk if you look at the damages associated with a loss in such a case?" asks Engert.

Simmon clarifies that AAM and the Biosimilars Council are not anti-patent. "We both support and applaud true innovation," she says. But like many in the industry, the group has seen too many examples of the U.S. patent system being abused and manipulated for the purpose of maintaining market monopolies — and this ultimately keeps drug costs high and slows innovation.

Attempting to rectify the country's patent problem will involve legislative change, specifically to the BPCIA, which sounds like a longshot, but Engert claims it's not as impossible as one might think.

> It's time for everyone to push it to the next level and really understand the risks comprehensively across all the functions — in particular, addressing the commercialization challenges.
>
> — Edric Engert

"If you look at the history of the

Hatch-Waxman Act, there was gaming of the system in the early days of the generic market in the U.S. and the Act was amended post-initial enactment to remove the loopholes that allowed a lot of the gaming," he says.

"The question is with Congress and the Administration: Can they be called to task to find potential legislative solutions to the litigation and IP barriers that currently are diminishing the adoption of biosimilars?" ***Additional shenanigans*** "Shenanigans" were famously linked the drug industry after FDA commissioner Dr. Scott Gottlieb reprimanded pharma companies that employ tactics to stifle generic competition, calling on them to "end the shenanigans."

According to Pfizer, these "anti-competitive behaviors incentivize the use of higher-cost originator biologics over biosimilars and create barriers to access to biosimilars."

Rebate traps and bundling are prime example of such shenanigans hindering biosimilar competition. Once a biosimilar is launched, some brand manufacturers will provide payers with rebates for branded products that are so large that even a biosimilar coming onto the market at a reduced price can't compete. Sometimes the brand manufacturers take it one step further, bundling rebates together for all products offered to payer. If the payer puts the biosimilar on the formulary, then the brand manufacturer will block the payer's access to rebates for all of the bundled products.

"As a biosimilar developer, even if you get FDA approval and wind your way through the patent thicket and emerge from the other side, it won't matter if you can't get market share," says Simmon. "It's really a way for the innovator to leverage the rebate system to block biosimilars from gaining traction."

While Gottlieb and the FDA have shined a bright light onto these anti-competitive tactics, putting a stop to these shenanigans is not within the agency's authority. As with many of the challenges faced by biosimilars, change requires legislative action from Congress.

UNIQUE CHALLENGES

While the systematic roadblocks faced by biosimilars are the most discussed, it's the unique challenges that sometimes prove to be the most shocking.

"Challenges can be unique to the behavior patterns of specific companies, the specific therapeutic area, the infrastructure and the distribution channels that are in place," explains Engert.

One example is the integration of biosimilars into oncology clinics. Biosimilars are seemingly a natural fit for oncology, where the efficacy of biologics has been undeniable, but their expense has been a significant burden, contributing to the rising cost of cancer care. Five of the seven commercialized biosimilars in the U.S. are oncology-related.

But in an environment where the treatments being prescribed are curative rather than supportive, and immunogenicity is a top concern, physicians have proceeded with caution when it comes to switching patients. A 2018 statement by the American Society of Clinical Oncology on the appropriate use of biosimilars in clinical practice stressed the need for post-market evidence to provide more data on the risks and benefits of switching from biologics to biosimilars.[3]

> There's a huge chasm between articulating an objective and actually coming up with an action plan that is executable and tha be successful.
>
> — Edric Engert

The payer system employed by most oncology clinics is an even bigger barrier. Engert points the "buy and bill" system often used in oncology clinics as an example of challenge unique to a particular treatment area. Buy and bill has been the primary method of distribution of specialty drugs, whereby oncology clinics purchase drugs from distributors to be dispensed in the clinic and then bill out to Medicare. The delta between what the clinics buy for and bill for makes up the majority of the clinic's income.

The shocking part? Sometimes the gross margin is up to 40 percent for larger clinics.

"The larger clinics that are able to negotiate larger rebates can enjoy a gross margin of 40 percent simply through buying and billing the products they dispense. And since their profits are tied to rebates which increase with higher prices, how can a biosimilar gain traction in such channels if they are offering notably lower prices than the originator?" adds Engert.

Oncology is currently leading the drug innovator pipeline, which means future opportunity for biosimilar makers. But manufacturers pursuing oncology biosimilars have to fully understand the space's unique challenges, including physician trust and the buy and bill landscape for clinics.

NEXT STEPS

While much of achieving the true potential of biosimilars hinges on better education and understanding, an action plan is still needed.

According to Engert, in order to advance biosimilar policy and regulations in the U.S., we need to turn aspiration into action.

There is a difference between having an aspiration and possessing the understanding of the market to a degree that results in a solution.

"The aspiration is there and the objective is well-articulated, but there's a huge chasm between articulating an objective and actually coming up with an action plan that is executable and that will be successful," says Engert. "You really have to know what all the incentives — and sometimes misaligned incentives — are for the adoption of biosimilars."

Forming a strategy

As a consultant, Engert has helped companies develop commercialization strategies for biosimilars by analyzing past behaviors of originator companies and creating different potential scenarios as to how originators might react to the launch of competing biosimilars.

"Patterns of behavior are incredibly important — it's not the number of competitors potentially on the market, but more which competitors are on the market," says Engert. "Some have very rational behaviors that are very much tied to standard economic objectives of maximizing profits, but some are more pursuant of strategic imperatives at any cost."

From there, biosimilar companies can form combating tactics to mitigate risks.

Due to their nascence, biosimilars often require a marketing launch similar to that of branded products.

"Focus on commercialization tactics is going to be key going forward but drugmakers will nevertheless still need to go out and educate as to what a biosimilar, the regulatory pathway, and manufacturing process are and why biosimilars can be trusted ," says Engert.

Technology-driven affordability Given the costly barriers to commercialization and the subsequent lack of biosimilar competition on the market, biosimilars do not offer the same average 85 percent price reduction (vs innovators) that generics currently offer.[4]

Affordability plays a roll in patient and payer acceptance, and some argue that biosimilars are not delivering low enough price reductions. In a recent analysis, Back
Bay Life Science Advisors polled U.S. payers representing large national health plans, and found they were reluctant to switch from the innovator therapy because they were not yet seeing the anticipated 30 to 40 percent reduction relative to the net price of corresponding biologics.[5]

As equipment vendors evolve to meet changing industry needs, new technologies and techniques that help maximize the efficiency of production labor and equipment can help biosimilar manufacturers save on manufacturing costs.

For biosimilars, the commercialization has proven to be just as complex as development. Univercells, a technology company delivering novel biomanufacturing platforms, offers up one potential solution. The company claims that their technologies can dramatically reduce Cost of Goods, thus enabling manufacturers to offer biosimilar products at competitive prices while still securing high margins.

"Our smart facilities are engineered to enable dramatic reductions in capital investment and CoG without compromising product quality," says Tania Pereira Chilima, product manager, Univercells. "These reductions are achieved through process intensification, process chaining and automation, as well as through the implementation single-use systems which reduces the utilities consumption."

For biosimilars, commercialization has proven to be just as complex as development.

Originally backed by an investment from Takeda Pharmaceutical Company, Univercells has a core focus on high-quality biologics for small to medium-size markets but the technology could provide relief fit for biosimilar manufacturers looking to keep costs down.

KEEPING MOMENTUM

Despite the pervasive uncertainty that plagues the U.S. biosimilar market, the market remains attractive. As novel biologic prices continue to rise, even when sold in small batches and at a discount, biosimilars have the potential to generate significantly high returns for drugmakers who learn to navigate the landscape.

For biosimilars, the commercialization has proven to be just as complex as development.

"Because of the complexity of the science and the nascence of the regularly pathway, people were understandably entirely focused the development, regulatory and manufacturing sides. Now it's time for everyone to push it to the next level and really understand the systemic versus unique risks comprehensively across all the functions — in particular, addressing the commercialization challenges," says Engert.

There is still work to be done on the regulatory side and the legislative side, and education of patients, physicians and payers should be ongoing. Beyond that, drugmakers who apply the same kind of rigor that they applied to develop and regulatory issues to commercialization, taking the time to understand what incentives are in place for each stakeholder and choosing their channels wisely, stand a better chance of success.

Biosimilars represent a significant catalyst for change in the healthcare industry, offering market-based, competitive solution to the issue of rising drug costs. If realized, they have the potential to create a more sustainable system, which could ultimately help more patients receive better care. "Biosimilars are a strategic imperative: something that requires focus, not just for the good of these companies to find substantial returns, but also to help create balance between the need for innovation and the need for a sustainable solution from a cost perspective," concludes Engert.

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Still got it

Tips and tricks to keep your older pharma plants riding high

By Meagan Parrish, Senior Editor

Everything you do in life catches up to you eventually. And just like the state of your complexion, pharmaceutical equipment loses its pep over time and cracks around the edges. Of course, these breakdowns are not only cosmetic. Without proper maintenance and occasional upgrades, old and faulty pharma equipment can increase the risk of contamination, which can trigger recalls and quality-related disruptions in production that don't just slow down work at one plant — they can also be a major contributor to U.S. drug shortages.

In pharma plants, age definitely matters.

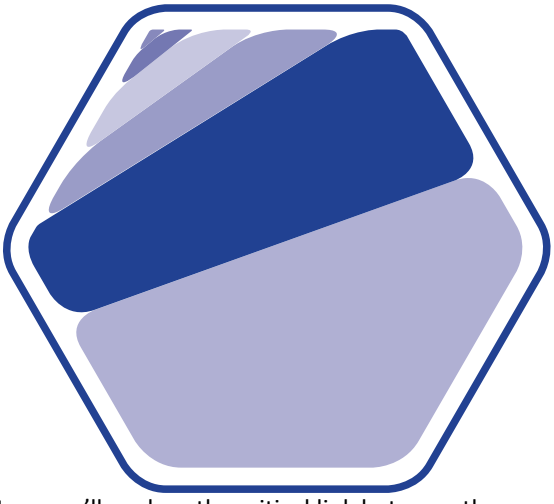
*Reason for drug shortages**

Ironically, there's no shortage of new equipment that manufacturers can buy to replace their older machines. Walk the floor of any industry trade show and you can easily get lost in the sea of snazzy new isolators, tablet presses, packaging robots, fill and finish machines — the list goes on. But in a pharma plant, pulling off this "swaperoo" is much more complicated than chucking out an old machine and then plugging in a new one to replace it. In fact, the process can be a regulatory quagmire that companies aren't likely to emerge from for at least a few years.

Manufacturing equipment is also a major investment and it's no wonder companies want to put off replacing them to get as much mileage out of their equipment as they can. On top of that, there can be uncertainty involved in trying a new kind of equipment and a learning curve that could lead to production disruptions. Overall, this

RAW MATERIAL	*1%*
NATURAL DISASTER	*3%*
SUPPLY/DEMAND	*8%*
DISCONTINUATION	*10%*
MANUFACTURING	*30%*
UNKNOWN	*51%*

**BASED ON A 2018 SURVEY OF DRUG MANUFACTURERS CONDUCTED BY THE UNIVERSITY OF UTAH DRUG INFORMATION SERVICES*



slow timeline for regulatory approvals and a fear of the unknown creates an environment that makes pharma companies wary of change.

"When it comes to new tech, no one wants to be the first to implement it — but everybody wants to be the fastest second," says Maik Jornitz, president and CEO of G-Con Manufacturing, and co-chair of the Parenteral Drug Association's (PDA) former Aging Facilities Task Force.

Yet, there are plenty of compelling reasons to give your aging facilities a needed facelift. Although the regulatory challenges are real, they're not insurmountable and can often be conquered in a way that's easier than companies realize. Also, putting off the process only delays the inevitable breakdown or a regulatory citation that's likely

to be more costly in the long run than an upgrade would have been.

Here, we'll explore the critical link between these manufacturing issues and widespread drug shortages, provide real-world tips on how companies can improve quality control in aging plants, and explain why it pays to update older facilities.

THE DRUG SHORTAGE LINK

Throughout 2018, the number of drugs and medical supplies in short supply in the U.S. hovered around 200. It's certainly not a new issue — back in 1999, the U.S. Food and Drug Administration launched a Drug Shortage Program to help conjure up solutions for keeping a healthy supply of the country's high-demand medicines. Yet, the problem continues to vex regulators and the industry.

Since Hurricane Maria hit Puerto Rico in 2017, creating production delays from one of the country's hot beds of pharma manufacturing, this natural disaster has often taken the blame for ongoing shortages. But manufacturing hiccups that hamper product quality have been shown to be a much bigger culprit of supply problems. The issue is particularly acute in aging facilities where

the use of older equipment can lead to higher rates of contamination.

A 2018 survey conducted by the American Society of Health-System Pharmacists (ASHP) asked pharma manufacturers to identify the cause of shortages, the mostcited known reason was “manufacturing” issues (30 percent). The FDA has also estimated that over half of injectable drug shortages are due to quality problems such as particulate contamination. According to ASHP, the rate of shortages is increasing and “severely impacting patient care and pharmacy operations.”

Of course, no manufacturer wants to produce contaminated products, especially for critical medicines. But unfortunately, the economics of producing some types of drugs doesn’t provide incentives for making the needed investments that could help avoid problems with impurities.

Although the drugs on the FDA’s shortage list include a wide range of treatments, the

majority are the most basic products for everyday patient care in hospitals, such as sterile water, lidocaine, saline, bupivacaine, and several kinds of opioids. These highdemand, older products also have low profit margins — making investments into production lines for the drugs less attractive.

Last November, the FDA held a conference on the issue of drug shortages and one panelist summarized the situation by saying that in short, the market doesn’t put a premium on creating a high-quality, reliable supply for these drugs.

HOW OLD IS TOO OLD?

There’s no easy way to define what makes a pharma plant officially over the hill. Some experts have estimated that most pharma facilities are designed to run well for about 20 to 25 years. And because all plants are in various states of aging — in regards to both equipment and the facility — it’s difficult to get a handle on how many plants in the U.S. have passed the 20-year mark. But Sue Schniepp, a distinguished fellow with Regulatory Compliance Associates, has seen plenty of first-hand evidence that operations in some plants look like they’re from a bygone era.

“The oldest line I’ve seen was about 50 years old,” she explains. “The company had a completely open line, and the only protection was a shower curtain.”

According to Jornitz, lines that are operating with frequent interventions, such as those susceptible to glass breakage, are at the highest risk of contamination.

“It’s important to take the human factor out of the equation,” he says.

Jornitz says that the fill lines are often the most vulnerable to contamination issues, but that older utilities, such as outdated water systems, can also put products at risk. Schniepp agrees that contamination risks go beyond equipment.

“It’s also in the floors if they’re not state-ofthe-art,” she says. “You have to also look at the ceilings — anywhere you’re bringing the walls and ceiling

> When it comes to new tech, no one wants to be the first to implement it — but everybody wants to be the fastest second.
>
> — Maik Jornitz

together there's a gap that could harbor microbes. It's one thing to put in a restricted access barrier system (RABS). But if there is microbial growth in some of the plant's older joints, what good have you really done?"

ANTI-AGING FOR PHARMA PLANTS

Naturally, regular maintenance and upgrades can go a long way in preventing some of these problems.

"All facilities are aging," Jornitz says. "However, when the company is reinvesting funds into the facility and have rigid maintenance or technology improvement cycles, the facility can age much slower."

One of the challenges, however, is that companies are often reluctant or unable to shut down their line to perform maintenance updates.

"When you're a contract manufacturer especially, sometimes you're running around the clock," Schniepp says. "But you have to shut it down to see what's wearing, what's tearing — and jump on it before it becomes a problem."

Despite the one-week shutdown that's typically required for a maintenance check on a company's line, Schniepp points out that it's better to spot cracks in the system when it's down because when it's running, operations can start to "go awry."

"Look at the line holistically and make sure the equipment is working together," she says.

Jornitz also recommends that companies use predictive maintenance to proactively improve the most important parts of the process steps. Additionally, he says that companies often neglect the importance of their equipment supplier relationships and don't keep track of the availability of spare parts for their machines.

"It's very important to get early warnings from the supplier that one of their equipment pieces is turning obsolete, so the end-user can act accordingly," he explains.

And putting off these kinds of assessments is likely to haunt companies in the end. Ronald Berk, chief technology officer and principal consultant at Hyde Engineering + Consulting, says that about half of the companies he's worked with on updating aging facilities are in some kind of regulatory trouble.

"We worked for a company that constructed their manufacturing facility in the late 90s, and the drug they produced was in such high demand that there was a capacity shortage, and they never upgraded the facility," he recalls. According to Berk, the company didn't want to slow down production of the drug, so it "hit the snooze button for 20 years," and never stopped

to maintain and improve quality at the facility. Then, after the FDA inspected the facility, the company ended up in a consent decree situation (where the company enters an agreement with the FDA to improve parts of their line that are in violation of regulations).

It's exactly this kind of regulatory scrutiny that should motivate companies to upgrade.

A TALE OF UPGRADING SUCCESS

One of the major challenges companies face when dealing with aging facilities is navigating the landscape of regulatory requirements. In particular, companies are reluctant to install new equipment that the FDA could consider a major process

PDA Survey on Aging Facilities

In 2015, the Parenteral Drug Association surveyed manufacturers about the state of their aging plants. Here are some of the most enlightening results:

What are the most pressing areas of modernization within your facility?

Facility (air/water systems, flow, finishes): **37%**

Process (filling, sealing, blow/fill/seal, chemical synthesis, etc.): **33%**

Analytics (sensor technologies, data software, etc.): **23%**

How long does it take to implement changes that require post approval?

2-4 years: **42%**

5-10 years: **29%**

0-2 years: **23%**

What is the average global regulatory cost per change requiring post approval?

$41-60k: **33%**

Greater than $110k: **17%**

$21-40k: **17%**

Do you have a formal plan to modernize your facility?

Yes: **48%**

No: **48%**

Do you have a formal plan to modernize your processes?

No: **68%**

Yes: **28%**

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modification under its Post Approval Change (PAC) rules. When this occurs, companies often have to revalidate their line, or go through all the tests needed for completing a prior-approval supplement (PAS), which can take as long as four years.

In 2014, the FDA set out to address this major regulatory hurdle by offering alternative avenues to updating technology. Now, the agency will allow companies to make updates to their operations without a PAS if the new technology is considered a "like for like" change with the older equipment. It's this route that Schniepp used to completely overhaul the line of one CMO where she worked — a major process she was able to get to the finish line in about two years.

"By doing 'like for like' you still have to do media fills and qualifications of the line, but you can do it without going through the PAS — as long as you don't change the footprint of the line," she explains. "It would be like upgrading the vanity in your bathroom."

Here are the major challenges Schniepp faced and how she worked with the company to overcome them:

Culture and communication: While working as the vice president of Quality for the CMO, Schniepp was tasked with updating a line that was the workhorse of the company, about 30 years old and produced 75 percent of its products. But in the depyrogenation tunnel, the cooling piping was above the products, which was causing fluid to sometimes drip into the vials. The contamination had cost the company approximately $28 million in lost products and triggered an FDA inspection. Yet, Schniepp still faced resistance to change.

"When you're a CMO, your culture is to please the client," Schniepp says. "When we wanted to upgrade the line, we had to coordinate between about 15 clients that had products on the line and get them all to agree on one approach."

According to Schniepp, not all of the clients thought the "like for like" approach would work. While some were worried about the

downtime involved in undergoing a potential PAS, others believed the changes could possibly be communicated to the FDA on an annual reportable. To get everyone on the same page, Schniepp made sure that she wasn't just talking to the quality department of every client, but also bringing each company's regulatory head into the discussions to get their input and help company leaders feel more confident in her plan.

Schniepp also ran her plan past the FDA to make sure the agency didn't have any major concerns with the approach

"What regulators really want to see is: Have you thought this out? Can you defend your case? And is your product going to be as safe and effective as it was before? That's how you win this game," she says.

Working in stages: Once it was time to implement the upgrades, Schniepp says it was all about planning ahead to make sure the company had adequate supplies of its products to offset downtime in operations. The company worked to replace the entire line during a four month period using the comparability protocol specifying before-and-after results for the product requirements for the manufacturing line being replaced.

All told, Schniepp says it took a total of two years to update the aging line. Although the company had to deal with about four months of downtime during the process,

it was much less of a burden to operations than it would have been to change the entire line under the PAS paradigm.

Training: Importantly, Schniepp says the company made sure to adequately train employees with the new equipment so that they could hit the ground running.

"We set up the line in a warehouse so the operators could work with it without making any products, because it was so different," she explains. "They had to learn how to clean the RABS and change out the parts. All of that was going on while we were developing the comparability protocol for shutting down and restarting the line."

PAIN POINTS

Just like when you're making updates in your home, Berk says that pharma companies often fail to plan for unexpected bumps in the road when revamping their operations.

"One thing that gets underestimated is that if you have an old facility and you start trying to fix things, you might discover other things that need to be fixed or some equipment might break," he says. "So some kind contingency plan for that is good."

According to Berk, companies also often overlook the life expectancy of their automation and control systems, which can be much shorter than mechanical systems.

Changeover to a new control system can also be more challenging than companies realize.

"The reality is that you need to spend quite some time testing and qualifying your control system, which can be very time consuming, and inevitably leads to a long downtime," he explains. "I've been at

sites where clients wanted to switch overnight. But the process can take up to a month — or half a year if it's a large facility."

THE ROAD AHEAD

There is hope on the horizon in the form of the industry's newest technologies, if pharma companies are willing to adopt them. The rise of single-use equipment, for example, could help lower contamination rates, especially because they allow companies to forgo much of the water utility systems needed to clean stainless steel parts.

There could also be changes on the regulatory front and the FDA has demonstrated a commitment to helping companies make needed upgrades.

PDA disbanded its Aging Facilities Task Force in 2017, but the organization has since launched a new task force aimed at addressing the challenges of Post-Approval Changes. One of the group's main efforts is to encourage the harmonization of the global regulatory approach to PACs so that companies don't have to undergo separate approval processes for upgrades in different countries. If other countries accepted an FDA approval, for example, it could shave years off of the process.

"The No. 1 question is: How can new, robust technology be implemented faster?" Jornitz explains. "But also, how can we help harmonize global regulations?"

But for too long, Jornitz says that the industry has used this regulatory hurdle as an excuse for not updating their facilities.

"Ultimately, running assets until they break down will cost much more than continuous improvements," Jornitz argues. And when it comes to dealing with the red tape, Jornitz says that companies that are updating aging tech have a strong case to make with regulators.

"If they can show that new technology improves patient safety and avoids drug shortages, I think regulators will listen," he says.

A deep dive into biosimilar interchangeability guidance

Will manufacturers want to go through the effort needed to jump into the biosimilar pool?

By Keith Webber, Vice President, Biotechnology, Lachman Consultants, and Bob Pollock, Senior Advisor and Outside Director to the Board, Lachman Consultants

I and their uptake in the market has been a discussion point since he issue of the use of biosimilars the first biosimilar was approved in 2015. On May 10, 2019, the FDA issued a long-awaited guidance on how a firm can demonstrate interchangeability of a biosimilar to its reference licensed product. The guidance is titled Considerations in Demonstrating Interchangeability with a Reference Product (which is a bit confusing as it applies only to biosimilars).

The agency notes that it will determine the biological product to be interchangeable with the reference product if FDA determines that the information submitted in the application or the supplement is sufficient to show that the biological product is a biosimilar to the reference product and "can be expected to produce the same clinical result as the reference product in any given patient." According to the agency, interchangeability also means that "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."

Such an interchangeability finding will mean that the biosimilar product can be freely substituted without the intervention of a health care practitioner that wrote the prescription for the reference product. This finding would be similar to a finding of therapeutic equivalence for a generic drug.

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FDA lists the scientific consideration for such a finding once a product has been found to be biosimilar as follows:

- Data and information needed to support a demonstration of interchangeability
- Considerations for the design and analysis of a switching study or studies to support a demonstration of interchangeability
- Considerations regarding the comparator product in a switching study or studies
- Abbreviated considerations for developing presentations, container closure systems, and delivery device constituent parts for proposed interchangeable products

The 23-page guidance discusses the parameters to be measured — some of which will depend on the complexity of the biosimilar, the indications proposed for the biosimilar, repeat dosing considerations, product-specific immunogenicity risk, use of switch studies, impact of post marketing data for a biosimilar that was approved without a finding of interchangeability, among others.

The guidance is very comprehensive in regard to the discussion of design of the various studies that will likely be required to support a finding of interchangeability, but the agency notes that the data necessary to support a finding of interchangeability will be evaluated and established on a case by case basis.

Much attention is devoted to describing how PK (pharmacokineti) and PD (pharmacodynamic, if available) data should be used, as well as the actual design elements of the switching study, the number of subjects, target population, as well as study analysis. The document also discusses the use of non-U.S. based reference products and the need for a bridge between the U.S. product and the non-U.S. based product. The FDA also points out the potential problems associated with a decision to use a nonU.S. licensed product and what additional considerations should be evaluated if a non-U.S. licensed product is used as the reference.

CHANGES IN THE FINAL GUIDANCE

While recognizing the final version of the guidance document is similar (highly similar?) to the previous draft from January 2017, a careful review found several useful and potentially significant changes in the final guidance.

- The final guidance is more definitive about the need for clinical studies to establish interchangeability. (However, was there ever really any question about this before?)
- Section V.A.3, *Totality of Factors to Consider in Assessing the Data and information Needed to Support a Demonstration of Interchangeability*, no longer includes the absence of a meaningful

"fingerprint-like" analytical similarity as a factor that would lead to a need for post-marketing data from the product's use as a biosimilar to support a demonstration of interchangeability. (Presumably, any product with high structural complexity and whose reference product has a history of rare, life-threatening adverse events would need to include post-marketing safety data to support a proposal for interchangeability.)

- The final guidance specifically states that the same bioanalytical methods should be used for testing PK and PD samples from the switching and non-switching arms of the clinical switching study. It also states that the validation of these assays should demonstrate that they perform similarly for both the proposed interchangeable product and the reference product.
- The final guidance added a paragraph in Section VI.A.1 *Study Endpoints* stating that "In cases where PK and/or PD are not adequately sensitive endpoints (e.g., products with limited systemic exposure, or for which PD effects are not measurable), sponsors are expected to propose and justify selected endpoints other than PK or PD."
- Section VI.A.2.a *Dedicated Switching Study Design* adds the incidence of immunogenicity and its consequences as factors to consider when determining the subject sample size for a switching study. In addition, this section has been modified to specify the primary endpoints for a PK switching study for an intravenously administered drug to be AUC_{tau}. For a subcutaneously administered drug, AUC_{tau} and C_{max} should be co-primary endpoints. With regards to PD studies, this section now includes a requirement for sponsors to propose appropriate margins and statistical analyses for their assessment.
- In Section VI.A.2.b *Integrated Study Design*, the recommendation in the draft guidance for "continuing of the proposed product arm (non-switching proposed product arm) from the inception of the study, through the duration of the switching portion of the integrated study, to the completion of the study" has been removed from the final guidance.
- Section VII, which was named *Use of a U.S.-Licensed Reference Product in a Switching Study or Studies*, has been renamed, *Considerations Regarding the Comparator Product in a Switching Study or Studies*. This renaming is a prelude to a significant change in the guidance. While the draft guidance lays out the argument against using a non-U.S.-licensed reference product and strongly recommended that sponsors use a U.S.-licensed reference product in switching studies, the final guidance repeats the concerns with using a non-U.S.-licensed reference product, but opens the door a wee bit by saying that "FDA believes that when supported by adequate data and information, it may be reasonable to use a non-U.S.-licensed comparator in a switching study." Of course, the big question in this regard is, "what constitutes adequate data and information?"
- Not too surprising is the culling down of Section VIII *Considerations for Developing Presentations for Proposed Interchangeable Products*. The draft guidance had a subsection of *"General Considerations"* and then went into great detail about threshold analyses for device components. The final guidance has scrapped the details (as well as an Appendix on Comparative Human Factors Studies) and simply presents the general considerations and recommends that sponsors

have early discussions with the FDA regarding their specific product presentation.

All in all, this final version provides greater clarity of the FDA's expectations for the studies that sponsors will need to perform and the data that they will need to submit to their BLAs when requesting a designation of "interchangeable" with the reference product. However, this field is still so new and still developing, and no guidance will eliminate the need for good communication with the Agency as a firm plans to move into this market. Will an FDA finding of interchangeability spur the confidence and acceptance of these products in the medical community? Only time will tell. Let's see how long it takes before a company jumps into the interchangeability pool!

The guidance is out, and the ground rules are laid down. It looks like a lot of work and it will be interesting to see if biosimilar manufacturers want to go through the required effort, given the fairly low uptake of approved biosimilars in the market.

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