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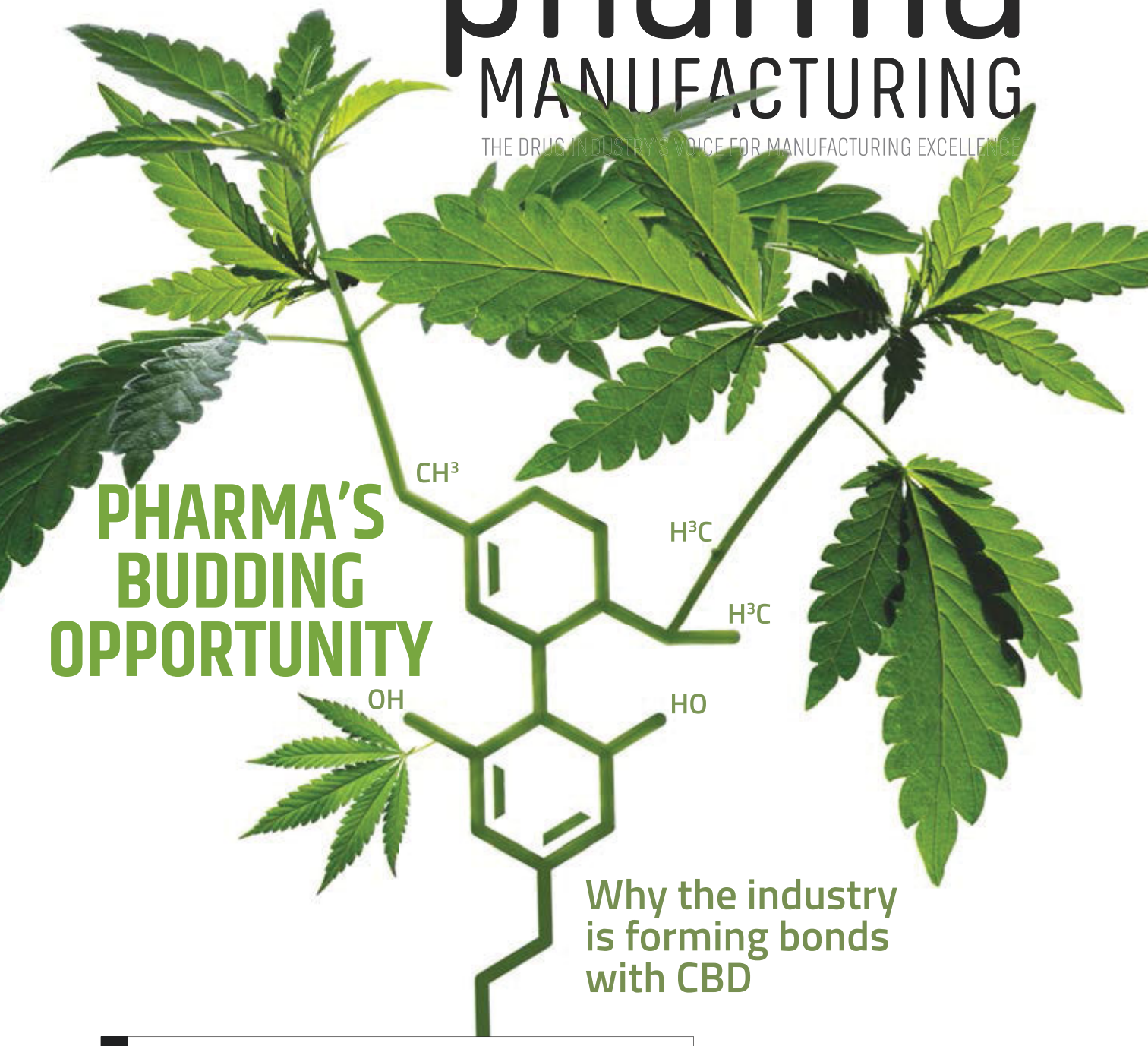

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Meagan Parrish
Senior Editor

Pharma's budding opportunity

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Joint ventures

Shared pursuits might lead to bigger rewards

Often, symbiotic relationships come naturally. I recently learned (via Animal Planet at 1 a.m.) that coyotes and badgers are frequently seen hunting together. This struck me as bizarre, as the two animals are generally competing for the same meal.

"Don't be fooled," said the narrator, "these two species are not friends." Apparently, it's simply a business arrangement. Coyotes have better eyesight and more speed than badgers, enabling them to spot small animals and chase them down. If the exhausted prey seeks refuge underground, the badgers tag in, using their incredible sense of smell to sniff out the rodents and powerful front claws to get to them. There are even stats: According to the National Wildlife Federation, coyotes with badger cohorts catch an estimated one-third more ground squirrels than solo coyotes.

This month's cover story focuses on the fast-growing cannabis industry. The cannabis industry and the pharmaceutical industry are not known for having a harmonious relationship. After all, the two are seeking out the same meal-ticket: cannabis threatens a very lucrative prescription painkiller market. For years, pharma has been criticized for lobbying to block the legalization of medical marijuana as well as quietly bankrolling anti-marijuana campaigns.

The passing of the 2018 Farm Bill has led to an explosion of over-the-counter CBD supplements (CBD is one of the primary, non-psychoactive compounds found in the cannabis plant) — and a widening acceptance among the general public of cannabis as an alternative to prescription pain meds.

Last year, the FDA approved Epidiolex — the first drug approval to contain a purified drug substance derived from marijuana. And there are currently numerous clinical trials involving cannabinoids underway. While many pharma companies are waiting for an FDA roadmap for CBD before pouncing on the looming market potential, others have begun to invest in cannabinoid APIs and pharma is slowly — albeit behind closed doors— teaming up with cannabis companies.

Despite their history of opposition, both industries have much to offer the other. Cannabis brings large consumer demands, new revenue and innovation, plus the ability to provide care to patients who, for various reasons, could not find relief from prescription drugs. CBD has been shown to be non-addictive, and is even being studied as a treatment for people with opioid-addiction disorders.

Pharma can offer CBD credibility and higher, more consistent standards — potentially increasing the quality and effectiveness of cannabis-based solutions. Pharma's well-controlled clinical studies and manufacturing procedures can ensure uniform strength and consistent delivery.

No one is going as far as to say the two industries have reconciled. But it seems that both are considering the benefits of sharing a table. As the coyotes and badgers have figured out, there is no shortage of squirrels. There are millions of patients around the world seeking relief from various ailments. A working cooperation means at the end of the day, everyone gets fed.

A dose of Washington comes to Chicago

CPhI N. America's keynote speaker explains what bipartisan bickering means for pharma

During his keynote address to a packed auditorium inside CPhI North America in Chicago this April, it became clear that Sen. Jeff Flake (R-Arizona) is one of the last of a dying breed. While combative politics continue to create gridlock inside the nation's capital, Flake has remained a rare stalwart of bipartisanship. Having served in Congress and the Senate for 18 years, Flake also offered historical insights into why Washington has become mired in partisan bickering.

Around the time Flake headed to Washington, he said it was common for legislators to live in D.C. and only return home for visits. Because politicians then spent more time together and got to know each other on a personal level, there was more trust and respect among the community of lawmakers.

"The level of trust that members of Congress have in each other has diminished because they don't know each other," he explained. "There's an old saying that you'll never question your colleague's motives if you know the names of their children."

All of that changed in the 90s, when lawmakers began staying in their home states more and commuting into D.C. when it was time to get to work.

"We're in a pattern now where members of Congress are trying to pass legislation with a narrow majority and then overturn the other party's legislation. It's not a good pattern to be in," Flake said.

Where do we go from here? When it comes to healthcare, Flake said that despite President Trump's continued desire to "repeal and replace" the Affordable Care Act, Republicans generally sense they have lost ground on this issue. Although Flake predicted that there could still be efforts to repeal the "individual mandate" within the law that requires all Americans buy into the system, the general consensus now is that Republicans don't want to look like they are against increased access to healthcare.

But one area where Republicans and Democrats have generally come together is on the issue of drug prices. Flake said he believes that the efforts to increase transparency for drug pricing will likely continue. But at the same time, lawmakers are aware that they don't want to stymie drug development.

"Whatever we do, we have to maintain incentives that drive the private sector to create the wonder drugs we still need," he said.

Jeff Flake
Senator (R-Arizona)

As Washington mulls different approaches to lowering prescription drug costs, Flake said he will continue pushing for bipartisan agreements that also include input from pharma industry trade associations, with an understanding that the business world banks on "stability and predictability."

By working with these various stakeholders, Flake said that lawmakers are more likely to craft sensible legislation that doesn't become vulnerable when the political pendulum swings a different direction.

"Legislation that endures is bipartisan," he said.

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How to boost your chances of winning an FDA drug approval

The commercialization of a new drug follows a rigid path and applying for FDA approval can be a minefield of challenges. Read this article for expert tips for nailing your application.

Q&A: Tablet production

Pharma Manufacturing sat down with a tableting expert to discuss common tablet manufacturing problems, pitfalls and fails — and how to avoid them.

12 steps for setting up a pharma cleanroom

Cleanrooms are an important part of manufacturing processes, scientific research and quality control. But setting up a cleanroom requires careful consideration both in the design phase, and then in how you use it.

Compressed air — the overlooked element of cleanroom specifications

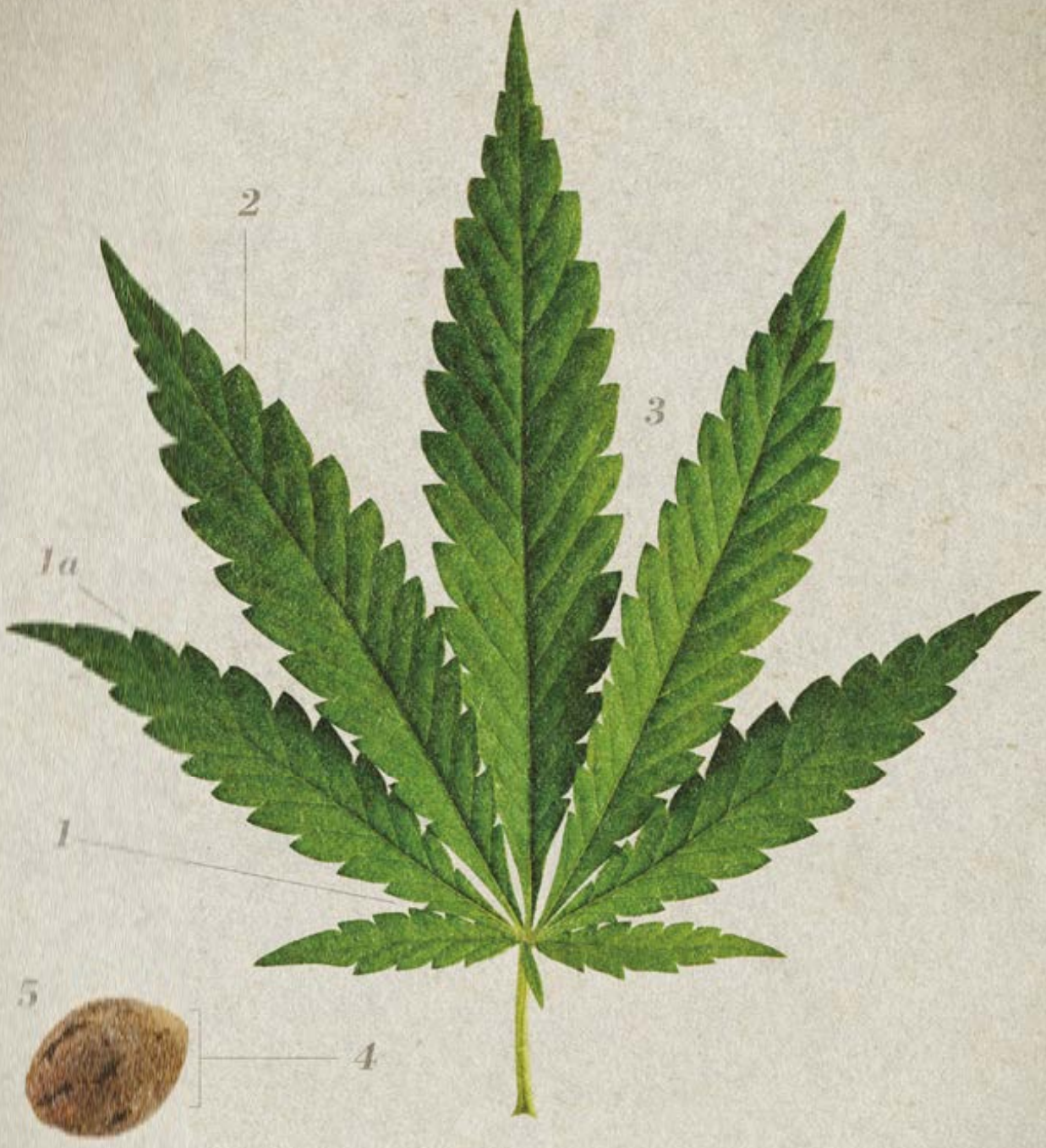
How applying cleanroom standards to compressed air systems can provide clarity and reliability.

Optimizing precision blending of tablets

A discussion of how tumble blender technology can enhance the speed and homogeneous blending of tablets and capsules with trace levels of additives.

Cowen analysts believe that CBD use will grow 10 percent among adults, totaling around 25 million consumers by 2025.

Read more about the **CBD market** on page 10.



Cannabis sativa L.

(cannabineae)

PLATE II

1. *Double spur vein to notch*
1a. *Single spur vein to notch*
2. *Main branch vein tangent to notch*
3. *Serrated leaves*
4. *Seed-bearing female plant, actual size*
5. *Cannabis sativa seed*

Meagan Parrish
Senior Editor

Pharma's budding opportunity

Why the industry is forming bonds with CBD

No single molecule has likely ever generated as much buzz in the wellness market as CBD.

Cannabidiol — commonly known as CBD — is one of the primary, non-psychoactive compounds found in the cannabis plant. A recent loosening of regulations for CBD has triggered an explosion of over-the-counter dietary supplements touting so many therapeutic uses for the molecule, it almost sounds magical.

Not long ago, cannabis products were widely viewed as a threat to the pharma industry, partly because of the competition they could pose within key therapeutic areas such as pain management. But these days, the smoky cloud of suspicion around marijuana and its derivatives has begun to clear, and pharma companies are getting poised to take a hit off the high-growth industry of CBD.

But even prior to new rules on the federal level, CBD sales were booming in parts of the country where marijuana is legal. In February, analysts at Cowen, a Wall Street investment firm, estimated that Americans spent about $2 billion on CBD products in 2018, mostly to treat anxiety, pain or sleep issues. By 2025, they predict that the market value will swell to $16 billion, partly fueled by rising beliefs in the effectiveness of cannabis compounds.

"In the 90s, when you read stories about it, the words 'medical cannabis' were always put in parentheses. But I don't think there's any question about the medical benefits of cannabis anymore," explains Philippe Lucas, vice president of global patient research and access at Tilray, one of Canada's biggest medical and recreational cannabis companies. "What I have seen over the last few years is that there is now a general acceptance of the overall comparable safety of cannabis, especially when compared to opioids, benzodiazepines and even OTC drugs."

In 2017, around 191 million prescriptions were written in the U.S. for opioids. Because many CBD users are looking for alternatives to prescription pain medications, the opportunity for that segment of the market alone is enormous.

Naturally, pharma companies have taken notice of the potential of CBD. In 2018, the U.S. Food and Drug Administration approved the first pharmaceutical drug with CBD as a primary component. According to ClinicalTrials.gov, there are now about 100 studies underway examining the impact of cannabinoids, the class of cannabis compounds that includes CBD, on a wide range of ailments — from heart disease to central nervous system conditions.

Yet, to a large extent, cannabis remains on the fringes of the pharma world. But there are signs that could be changing.

Last year, Sandoz dove into the space when it struck a development and marketing agreement with Tilray — the first deal of its kind between a Big Pharma company and a cannabis partner, and a sign of a turning point between the two industries. More deals are likely on the way. All throughout the CBD supply chain, scores of companies — from drug development to delivery — are readying themselves to hook up with pharma's top dogs so they can jointly cash in on the growing "green rush."

The wonder weed

It's well known that marijuana was used as a medicinal plant for centuries throughout the world. But in the 1930s, American attitudes towards marijuana soured as its use became increasingly associated with immigrants and minorities. By 1937, the growing anti-pot hysteria triggered new regulations that effectively made marijuana illegal for medical and recreational uses.

In the 1990s, however, the medical potential of this ancient plant crept back into the healthcare consciousness as patients began smoking it to combat the harsh side effects of chemotherapy, among other health issues. Although the primary focus was on potential of THC (tetrahydrocannabinol, the compound in weed that produces a high) to treat a variety of ailments, the flurry of cannabis research has also brought CBD to the forefront of drug innovation.

What is it about CBD that makes it such a potent weapon against a wide variety of health troubles? According to Ann Allworth, a former medical school professor with a PhD in biomedical sciences with a focus on cell biology, it's all about how marijuana compounds target the endocannabinoid system, which overlays every system in the body.

"This is what's unique. The endocannabinoid system coexists with cells in all systems of our bodies," Allworth explains. "This includes reproductive, endocrine, cardiovascular, urinary, nervous, immune, skeletal, muscular and even our skin."

The discovery of the endocannabinoid system started in the 1960s when an Israeli researcher set out to decipher why weed made people high and laid the groundwork to scientists finding receptors now known as CB1 and CB2 all throughout the body. Allworth says that when marijuana compounds like CBD hit those receptors, they can help restore balance to the body's different systems when the associated endocannabinoid system is impaired. Unlike many conventional medicines for tough-to-treat diseases that only ease symptoms, Allworth says that activating these receptors can, in many cases, fix the root of the problem on a cellular level.

"The bottom line is that the endocannabinoid system works to create balance in all systems of the body," she says. "This is why CBD works for a wider range of conditions than any other medicine known."

Like so many die-hard converts in the CBD industry, Allworth's foray into cannabis products started with a personal ailment. After being diagnosed with an autoimmune disease and told by her doctor that she would have to be on steroids for the rest of her life, Allworth went hunting for alternatives. Friends eventually steered Allworth in the direction of CBD, which she says, caused her symptoms to vanish. Now, Allworth has launched a new company called Cannabis Education Solutions, which is aimed at teaching healthcare professionals about the endocannabinoid system and promoting curriculum reform to medical schools so that more incoming doctors understand the role it plays in the body.

"I think one reason it's not taught is because when some people hear about the endocannabinoid system, they think it's something the medical marijuana industry cooked up to sell their stuff," she explains. "But there shouldn't be any stigma around CBD. There is fundamental evidence that CBD can be helpful for many diseases."

From the streets to the suites

Like Allworth, Marcelo Reinhardt, the director of business development of C2 PHARMA, an API manufacturer, became a believer in CBD after feeling the effects for himself.

"I have back pain and had been taking painkillers for at least three or four years," he explains. "I started using CBD oil out of curiosity and now I haven't taken any painkillers in several months."

Established in 2014, C2 PHARMA has begun unveiling the latest offering in its API portfolio: highly potent and pure CBD. C2 PHARMA hasn't started selling CBD just yet, but the company has locked its supply chain into place — from cultivation to distribution — and is readying itself to be a go-to source for pharma companies looking to purchase high-quality CBD for drug development and manufacturing.

"We want to position ourselves as one of the leading sources for CBD, and all other cannabinoid APIs for the pharma industry," he explains. "We will extract and isolate the APIs under all the compliance guidelines for pharma and will be ready once they want to launch products with CBD."

Therapeutic targets

Conditions being tested in clinical trials with CBD

- Pain
- Post-traumatic stress disorder
- Arthritis
- Schizophrenia
- Autism spectrum disorder
- Anxiety
- Heart failure
- Substance abuse disorder
- Epilepsy
- Glioblastoma
- Crohn's disease

C2 PHARMA, based in Luxemburg, currently has more than 100 customers for its APIs, including over 15 Big Pharma companies. Reinhardt says that even though rules around CBD are still prohibitive on a global level, the company is focusing on establishing itself in the regulated market, where the potential is biggest.

"I think it's going to be huge," he says. "And there are a lot of players trying to get a piece of the action now."

According to Reinhardt, dietary supplements made by the hundreds of companies that have popped up to produce CBD oils, gummy bears and more, are the "low hanging fruit." The real ball game is in the pharma-sphere, where entry is more difficult but the rewards are higher. Now, many companies like C2 PHARMA are looking at ways to expand their pre-existing portfolios to include CBD offerings.

California-based CURE Pharmaceutical, for example, has developed an innovative oral film technology that the company believes could represent the future of improved drug delivery. The company already offers several high-potency dietary supplements and has established a partnership to manufacture a generic form of Viagra using its CUREfilm technology. Recently, CURE also broadened its Drug Enforcement Agency license so that it can research cannabis plant extracts and CBD.

Although there are a lot of entryways into the CBD market, Jessica Rousset, chief operations officer at CURE, says that the company's ability to get high doses of medications into easily dissolvable films will give CURE a niche edge in the booming market.

"The future on the cannabis side is not in cultivation — that's the race to the bottom," she says. "The future is in drug delivery."

Rousset says that CURE is not yet disclosing the details of any partnership discussions with pharma companies, but they are happening. Currently, however, the U.S. industry is still stymied by regulatory confusion over CBD and concerns that new FDA rules could alter the landscape of the market.

"We have a lot of companies coming to us wanting to make CBD products," she says. "But we are an FDA-registered facility — we don't operate under state laws — so we are actively pursuing the manufacturing of CBD products within federal guidelines."

Dazed and confused

Although rules around marijuana are still a messy patchwork of contradicting federal and state regulations, the U.S. is at least trying to develop a sensible framework for CBD.

One major turning point came in December, when President Trump signed the latest Farm Bill into action, which included a provision that legalized CBD when it's derived from hemp under specific growing conditions (with a low concentration of THC). The bill also preserved the FDA's authority to regulate consumer products containing CBD. Although cultivation, distribution, and possession legality is determined by state and federal laws, the FDA is tasked with deciding if CBD pharmaceuticals are safe for consumption, how OTC CBD products should be labeled and importantly, whether CBD should be treated as a dietary supplement or a pharmaceutical ingredient.

The issue took center stage in early June when the agency held a public hearing for CBD stakeholders in

an important first step towards deciding how to sheriff the "wild west" CBD market. From the onset of the meeting, it was clear that the FDA has a daunting task in front of it — and the stakes are huge.

So far, the FDA has been looking the other way as companies add CBD to food products and has only cracked down on a few dietary supplement manufacturers for potentially making false labeling claims. But because the FDA approved a pharmaceutical drug derived from CBD last year — GW Pharmaceuticals' treatment for rare and severe forms of epilepsy in children called Epidiolex — the agency could decide that CBD should only be treated as a drug and not allowed in OTC products. For now, the agency will likely attempt to find a balance between allowing continued access to OTC CBD without undermining its established clinical trials process for pharmaceutical drugs.

But after 10 hours and presentations from over 100 speakers from various corners of the CBD industry including manufacturers, healthcare professionals and patients, the hearing left many feeling more lost than ever. Although many speakers touted the compound's safety, several also warned about the inherent dangers of marijuana and a lack of credible research on CBD. The agency's acting commissioner, Ned Sharpless, said in his opening remarks that although the FDA recognizes the intense public interest in CBD, there are still "critical questions" about the safety of cannabis compounds.

The only clear consensus was that everyone wants the agency to find its footing in this market quickly. But so far, the FDA has not laid out any kind of roadmap for making regulatory decisions for CBD and the market could be waiting for months (or years) before it's operating under clear rules.

Oh Canada

While the U.S. marijuana market stumbles along, unsure of what the future holds, Canada has surged ahead with a legal cannabis industry that will rake in an estimated $7 billion this year. It's no surprise then that Canada has become the home of some of marijuana's biggest players, including companies that are blazing new trails into neglected niche therapy markets.

Ontario-based Cardiol Therapeutics, for example, has become one of the only biotechnology companies focused on developing cannabinoid-based treatments for the massive heart failure market. David Elsley, the company's president and CEO, says he first became interested in CBD after coming across research that discussed the role of using the compound to fight diastolic heart failure — a segment of the cardio drug market that hasn't seen a significant treatment advancement in 30 years.

In particular, Elsley says that what makes CBD effective in treating conditions such as heart failure is its anti-inflammatory properties and the way it works through the immune system to relax blood cells and lower blood pressure.

> **CBD works for a wider range of conditions than any other medicine known.**
>
> — Ann Allworth

"When we look at this molecule through a heart-disease lens, we see a protective molecule," he explains.

Cardiol is now working with two pharma companies, Dalton Pharma Services, a CDMO with expertise in cannabinoids, and Noramco, which specializes in production for controlled substances, to help bring its CBD-based treatments to market. Currently, Cardiol is in the process of commercializing a pharmaceutical CBD product with zero-detectable THC — what Elsley calls the "new gold standard" — that the company will market in the EU, Canada and Latin America.

For the U.S. market, Elsley says the strategy is to work with the FDA to win approval for its heart failure medication, following the same regulatory process as the epilepsy treatment that got the green light last year.

Scores of other biotech companies have also jumped into the race to create pharma-grade CBD treatments, with a new focus on synthesizing the molecule from sources other than marijuana (which might allow companies to bypass that tricky regulatory landscape).

Last year, Boston-based Ginkgo Bioworks, which has worked with big name companies like Bayer, made a $122 million deal with a Toronto-based cannabis producer called Cronos, to harness marijuana's DNA and make lab-grown cannabinoid strains. Ultimately, the goal is to target the pharma industry with lower-cost cannabinoid compounds with medicinal potential.

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But the biggest deal in the industry so far was struck between Sandoz, the generic arm of Novartis, and Canada's Tilray. Last year, Tilray became the first cannabis company to have an IPO on the U.S. stock exchange, and was one of the top 10 performing IPOs of 2018.

As part of its agreement, Tilray will leverage Sandoz's industry know-how to educate Canadian physicians and pharmacists about medical cannabis. The companies will also develop and co-brand Tilray's extract products — and according to Lucas, having the Sandoz logo on its products is like winning a seal of approval in the eyes of healthcare professionals.

"This raises the level of confidence that insurers, doctors and prescribers have towards our cannabis products," he says.

The partnership also represents the potential of what pharma can do to transform the world of CBD.

The pharma factor

Although the CBD market is busting at the seams, it still lacks an air of legitimacy on a mass scale. At the recent FDA hearing, several speakers pointed to studies that have shown that OTC CBD products often don't contain the exact dosing that their labels promise. As more companies crowd into the CBD market and rush to get products into stores, these low-quality offerings could soon rattle consumer confidence, and send patients looking for more reliable options. This, of course, is where pharma comes in.

In the risk averse world of pharma, where high-purity is paramount, drugmakers have an opportunity to leverage the industry's manufacturing standards and edge out lower-quality products. The consumer demand is there. But what the CBD industry needs is higher standards, especially if it's going to win over healthcare professionals.

"We ultimately benefit from pharma taking part in this industry and removing the remaining stigma around cannabis," Lucas says.

One of the biggest challenges Allworth sees for pharma entering more wholeheartedly into the cannabis space is that the industry might have to change its mindset from researching single molecules to looking at the entire plant. Marijuana is thought to have over 100 cannabinoids, and many healthcare professionals believe that they work best when taken together.

"I think the most beneficial way is with all the terpenes, flavonoids and cannabinoids together," Allworth says. "Because Big Pharma is focused on single molecule remedies, it's going to be difficult to achieve the same results with just CBD."

The CBD market may not be pharma's typical gig but the opportunities to work with smaller drug developers to commercialize innovative products are piling up. Although none of the companies interviewed for this article would disclose specific details about any partnership discussions they may have underway, they all showed a strong interest in buddying up with players in pharma to help commercialize their goods.

There's also a lot of hope that pharma won't just help these companies soar to new heights, but improve access for patients as well.

"We understand that with pharma, we're going to see more refined cannabis products enter the market. But they could improve patient experiences or maybe even help reach an older population that has never tried cannabis," Lucas says. "With the formal medicalization of this substance, I honestly hope that patients will have more access to these whole plant medicines."

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Patterson Shafer
Managing Director, Healthcare and Life Sciences, Grant Thornton

Perfecting CAPA

"Flawless" may not exist on the plant floor, but reviewing your quality process can save money and lives

Many years ago, while working on developing a Quality Management System for a large automotive company, we heard a story about how the company had perfected Corrective Action, Preventive Action (CAPA). The company had a clearly defined, cross-functional process with a very useful quality tool kit containing templates for data collection and root-cause analysis that were extremely effective for brainstorming solutions. The process also routinely included a detailed cost analysis. Executing the CAPA process was costly — to the tune of several hundred thousand dollars — but very effective.

At one point, the company had identified a problem in one of the paint shops. The problem was recurring, and causing significant rework. Consequently, the shop manager opened a CAPA. The shop used the tools, collected the data, performed the root-cause analysis, and fixed the problem. The issue never recurred in that shop. However, the same problem occurred in 24 of the company's paint shops around the world. Each shop, independently, followed the CAPA process and solved the problem. However, the CAPAs alone cost the company more than $10 million.

If all sites had visibility into the first solution, the company could have saved millions. Despite "perfecting" CAPA, the company still struggled with the high costs associated with the process. There is some irony in seeking to perfect a process that, by definition, points out imperfections; however, taking a well-structured approach can help pharma companies create a more effective CAPA process that pays off in the end.

Is there a problem?

Many companies have recognized problems with volume and cost, as well as ineffectiveness of the CAPA process. The cost of the CAPA process alone, not including remediation, can run into the hundreds of thousands of dollars per CAPA. Companies can find they generate so many CAPAs that CAPA processing backlogs develop. One senior executive visited a plant and found 15 overdue CAPAs. Such backlogs create compliance issues and can end up as a finding in an inspection report.

As part of its Case for Quality program, the U.S. Food and Drug Administration (FDA), in partnership with the Medical Device Innovation Consortium (MDIC), is currently sponsoring a working group to improve the CAPA process. The initial focus of the working group is to develop a reference triage process that will allow companies to address non-conformances and other issues with confidence — generating CAPAs only when patient health and safety may be at risk or other recognized criteria are met.

EXHIBIT 1

Sample level 1 CAPA process

Even with manageable numbers, problems with implementation and overall effectiveness remain an ongoing challenge. Some companies rush to close CAPAs prematurely to remain in compliance with their Standad Operating Procedures (SOPs). Others fail to include appropriate stakeholders in the investigation and planning process — further exacerbating problems rather than successfully addressing them.

The CAPA process

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidance refers to a structured approach. The specific process will vary from company to company, involving different parties and leveraging different tools, but will include the same main elements (Exhibit 1).

The process starts with any of a number of triggers. The basic criteria are related to product quality, business efficiency and, in life sciences companies, patient health and safety. Initiation refers to capturing and recording information related to the CAPA, including cause, severity, stakeholders, and target outcome, among others.

Investigate: This involves collecting data to understand the problem and root-cause analysis to make sure the solution addresses more than the symptoms of the issue.

Form solution: Correct the immediate issue (corrective action) and prevent recurrence (preventive action).

Implement: This may require initiating a product or process Change Control, which may trigger a regulatory variation filing (contributing to the high cost of CAPAs). SOP revisions will most likely be necessary, requiring communication and training.

Monitor effectiveness: Note that the process does not end with implementation. Companies can close the CAPA in the system. However, CAPA effectiveness must be monitored on an ongoing basis. Only after the corrective and preventive actions have demonstrated effectiveness can the process be considered complete.

When should CAPAs be initiated?

The process starts with occurrence of any number of triggers including a finding by a health authority, a significant process deviation, recurring non-significant deviations, adverse events, complaints, or a Health Hazard Evaluation. The company should have clearly defined criteria for initiating a CAPA, applied uniformly across the enterprise. Given the significant time and cost associated with a CAPA, determining a reasonable threshold is important.

CAPAs should be entered into a system with sufficient detail to support effective investigation and reporting.

Generally, compliance-related issues are worthy of a CAPA. Minor deviations, however, would not warrant a CAPA. Recurring deviations that result in rework should trigger a CAPA, as should deviations that could have an impact on patient safety. A Form 483 and warning letter findings are definite triggers. In many cases, management may trigger a CAPA coming out of a periodic Quality Management Review to address an issue or as part of continuous improvement.

The right number of CAPAs

Unfortunately, there is no right number. Companies with complex or high-risk products may initiate more

CAPAs than companies with simple manufacturing processes. Companies with mature quality systems and processes can expect fewer CAPAs.

As mentioned previously, some companies are overwhelmed with volumes of possibly unnecessary CAPAs. Other companies try to avoid CAPAs, fearing raising red flags with authorities and wanting to avoid the costs associated with the CAPA process. Authorities will expect to see numbers that reflect the level of recurring complaints, inspection findings or other issues.

CAPA tools

There are two categories of tools — one is the QMS solution that would be used to manage the CAPA process, where CAPAs would be initiated and tracked. The other tools are the traditional methodologies used to support investigation: histograms and Pareto charts to support issue identification, and Ichikawa or fish-bone diagrams to support root-cause analysis.

Enterprise QMS solution: As the name implies, this is the primary solution used to support the Quality Management System. Companies often try to use one system to manage all quality processes — deviations, inspections and inspection findings, complaints, change control and CAPA. One advantage of a singular system is that the processes can be easily referenced. Data from deviations or other quality issues can be transferred to the CAPA, saving time and allowing for traceability.

While some small companies rely on paper to manage the process, they are likely to hold on to paper much longer than advisable. CAPAs should be entered into a system with sufficient detail to support effective investigation and reporting. An enterprise quality IT system would have potentially allowed the automotive manufacturer in our previous example to gain visibility at the enterprise level while avoiding millions of dollars of wasted effort. CAPA initiations should be reported regularly as part of standard operational monitoring and periodic management reviews. Another reason to leverage technology over paper CAPA management: There are several software-as-a-service (SaaS) quality solutions that are reasonably priced and very effective.

Quality toolkit: A histogram charts occurrences over time. This gives a sense of frequency and impact of an issue. The histogram can also support root-cause analysis by relating peaks with other events occurring at the same time.

Pareto charts can be used to capture types or categories of issues. By graphing the issue counts by category, one or more categories will emerge as the "winners" and allow teams to focus on the issues of greatest concern.

The Ishikawa diagram is a brainstorming tool that provides a structured approach to exploring possible root causes. The diagram resembles a fish skeleton and is also known as the fishbone diagram. Each arm represents a possible root cause. As team members hypothesize causes, they add potential contributing factors to be explored (Exhibit 2).

A corrective action may be taken to provide a stop-gap solution — to allow a process to be run or a batch to be released. Preventive actions are intended to be long-term solutions. These solutions should be implemented only after undertaking a rigorous root-cause analysis, lest the fix not fully prevent recurrence and the CAPA process be repeated.

Defining CAPA

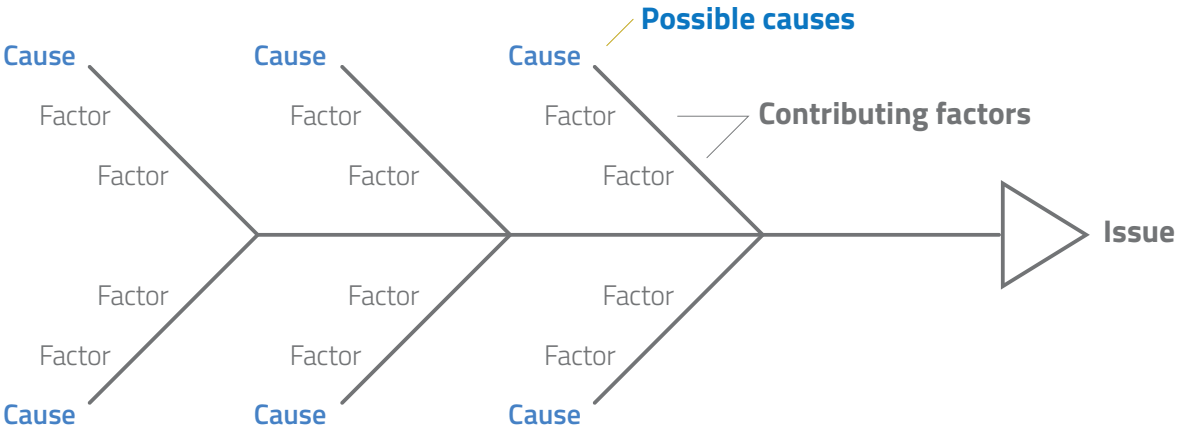
Corrective Action, Preventive Action is a core part of any pharmaceutical Quality Management System (QMS) . The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance states:

The pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring.

A structured approach to the investigation process should be used with the objective of determining the root cause. The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk, in line with ICH Q9. CAPA methodology should result in product and process improvements and enhanced product and process understanding.

EXHIBIT 2

Ishikawa diagram



CAPA cost/benefits

Quality is a high-stakes business — not only measured in dollars, but more importantly, impacting patients' lives. Poor quality is measured in seven figures, or more. Label-related recalls alone can cost pharma companies more than $100 million a year. Industry quality executives have estimated an average cost of $10 million for a Form 483 finding. A warning letter can set companies back approximately $200 million, and a consent decree could cost upwards of $1 billion.

CAPAs are expensive as well, but are clearly preferable to the significant costs of noncompliance. As mentioned, the process alone can consume hundreds of hours. Implementation of a solution requires its own impact assessment. The Change Control process may be involved, which can lead to a regulatory impact assessment and variation filings in a number of countries.

All this points to the pursuit of the goal of "Right First Time" and continuous improvement. Assuming CAPAs are initiated prior to a health authority finding, they are executed in the spirit of continuous improvement, rather than under duress of regulatory oversite.

Measuring effectiveness

Measurement is foundational to the CAPA process. Measurement of process and process outputs often trigger the CAPA. Recurrence, trending, financial impact and health hazard evaluations are all factors driving initiation.

Once initiated, managers track progress through the CAPA process. The primary focus is on CAPA closure timeliness and the number of overdue CAPAs. More mature companies track and report financial impact and other data such as cause, manufacturing site, and products to provide better insight, improved forecasting of CAPA durations and improvement of the CAPA process itself.

Of course, one of the primary measures should be CAPA effectiveness. Ineffective preventive action can lead to hemorrhaging of cash as well as potential threats to patient safety.

Perhaps there's no such thing as a "perfect" CAPA. Indeed, perfect would be achieving optimal results the first time through, eliminating the need for CAPAs altogether. With changing regulations, evolving technologies and a mandate for continuous improvement, this day will likely never come — yet pharma must continually strive for better quality management processes.

Michael Francis
Global Product Manager, Emerson Automation Solutions

Retrofitting batch with single-use

Single-use technologies offer multiple benefits for those who can overcome instrumentation challenges

The pharmaceutical industry has long relied on stainless steel bioreactors for processing batches of intermediate and final stage products. While these vessels work well in many applications (especially for large batches of 5,000 liters and up), there are many issues better addressed by utilizing single-use bag bioreactors.

This article will discuss the advantages of single-use technologies, and will show how instrumentation challenges can be overcome, particularly for measuring critical process parameters such as pH and dissolved oxygen (DO). These advantages are driving many pharmaceutical manufacturers to retrofit the bioreactor portion of existing processes to single-use.

The allure of single-use

Process and manufacturing industries strive to increase throughput and therefore improve economies of scale. In pharma manufacturing, sometimes this paradigm is superseded by a need for flexibility, along with reducing cleaning and sterilization costs.

Traditional fixed-asset stainless steel technology (SST) is how pharma manufacturing has typically scaled-up operations. Newer single-use technology (SUT) represents an alternate approach, addressing problems with SST and delivering additional benefits.

Even ignoring the initial costs of SST equipment fabrication and installation, operating costs remain quite high since cleaning and sterilizing operations require significant support infrastructure. Equipment and fittings must be cleaned-in-place (CIP) or cleaned-out-of-place (COP) for each batch. CIP/COP consumes large amounts of water and chemicals. The chemicals in question — such as acid, caustic soda and detergents — introduce handling hazards. Much of the water must be of water-for-injection (WFI) quality, which is energy-intensive to produce.

After cleaning, SST equipment must be sterilized-in-place (SIP) with steam, another energy-intensive operation. Occasionally, even after all cleaning operations are properly performed, residue from prior batches remains and can negatively impact the quality of subsequent batches.

Process instrumentation, especially analytical elements, are relatively fragile compared to the equipment, so extra effort is required to protect them during these cleaning

methods. Even so, instruments can still be damaged or destroyed, and often require frequent recalibration or replacement.

From a physical standpoint, once SST equipment is installed, there is little or no plant layout flexibility. Small batches and trial runs are frequently not feasible or cost-effective. Looking forward, SST is not well suited for supporting the future wave of small batch and personal medicines.

Systems using SUT elements, such as disposable bioreactor bags, obviate many of the problems experienced with SST equipment and provide other advantages. Chief among these is the fact that single-use bioreactor bags arrive pre-assembled and pre-sterilized from the original equipment manufacturer (OEM). The bags do need to be enclosed in some form of support structure, which is quite minimal compared to traditional construction.

No WFI, CIP, COP or SIP systems are needed to prepare the bags. This provides large energy and emissions savings, especially the relief from needing steam generation for SIP. After a production run is completed, bags are not reused, but are instead sent back to the OEM or elsewhere for recycling or incineration.

With a shelf life of two or more years, single-use bags allow users to easily gauge their stocking needs and deploy new bags quickly. Bags are offered with dual fittings for measurement redundancy and can achieve mixing either with integrated stirrers or by installing them on rocker tables.

Single-use methods give end users more flexibility for scaling up and down, as opposed to being constrained by significant amounts of fixed installed infrastructure. A SUT facility can be built much quicker than a new SST plant, and initial capital costs are much lower.

Traditional fixed-asset stainless-steel equipment requires copious amounts of water, chemicals and energy to clean and sanitize, and instrumentation is often damaged when these processes are performed.

Single-use issues

Single-use methods do introduce challenges, however, especially with the integration of measurement instrumentation in the bioreactor. The sensor element portion of an instrument must contact the product via a fitting in the single-use bag, so this interface must be carefully evaluated. The instrument's other main component, the transmitter, is not in contact with the process media and thus remains the same for both traditional and single-use processing methods.

Since single-use bioreactor bags are sterilized using gamma radiation, all materials and devices must be able to withstand this procedure. Some sensors use modified designs compared to traditional versions in order to survive this sterilization, so users may have concerns whether these sensors perform as well as traditional devices. This uneasiness was reinforced by original single-use sensors which experienced high drift. However, the newest generation of sensors are improved to be three to five times better than existing SUT sensors, eliminating this area of concern.

One way of integrating and preinstalling single-use pH sensors into bags utilizes a dry storage technique. Unfortunately, some pH sensors of this type can't be tested until the bag is filled with product and committed to production — far too late to replace a faulty sensor. Another concern is that some preinstalled sensor elements may have a shorter shelf life than the single-use bags, negating the benefit of a long bag shelf life. For measuring electrodes, any exposed glass during storage must be avoided to prevent mechanical contamination.

The physical fittings, also called ports or adapters, used to install

sensors into single-use bags have also presented challenges. Fittings must be mechanically designed to meet aseptic requirements. Since the instrument fittings are integral with the bag, selecting the right fitting materials to withstand gamma radiation and maintain aseptic properties is critical. This is verified by conducting extractables and leachables (E&L) testing to ensure the materials will not contaminate batches, even after gamma radiation. Testing is expensive, and compliance can be difficult to achieve for some vendors.

This means that suppliers must choose premium materials with clean natural profiles, typically United States Pharmacopeia (USP) Class VI-tested and free of animal derived ingredients (ADI). Materials must be selected to meet high biocompatibility standards, and USP Class VI materials offer an excellent, well-understood benchmark for all of the different types of polymers used on SUT devices. From an end user standpoint, instruments should connect to SUT bags just as traditional instruments do.

End users want the flexibility of single-use methods, but they want to achieve process control in the same way as with stainless steel methods, with no degradation in performance. These goals can be met by employing the latest measurement technologies.

Focus on pH

Since pH is a critical process parameter for any bioreactor, users need sensors with zero drift and a long shelf life. Traditional pH sensors are high maintenance, especially when installed where CIP or SIP is performed. For these locations, the sensor sometimes must be removed, sterilized separately, then reinstalled for these operations.

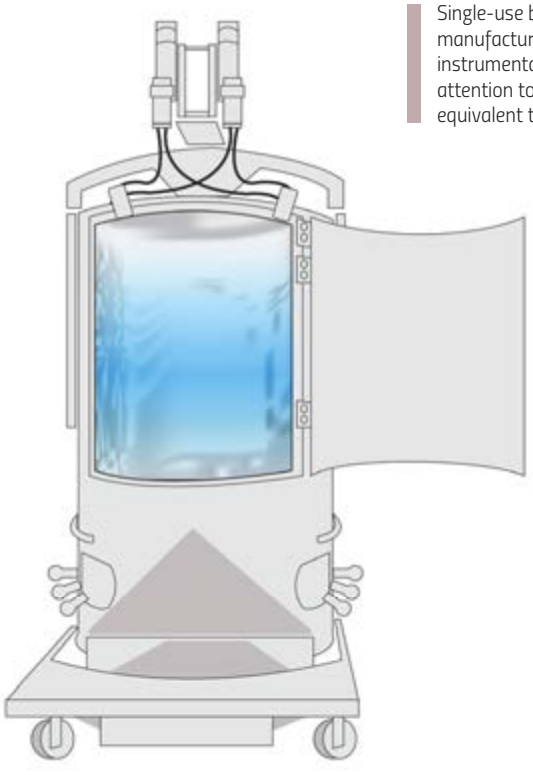
For single-use applications, the entire pH sensor must be suitable for a whole production run because it is in direct contact with the process media. Traditional measurement techniques use a glass electrode, and SUT instruments using the same method have similar accuracy.

One significant difference is that traditional sensors have a shelf life of only six to 12 months, far below the shelf life of the SUT bag they would be preinstalled into. Emerson has overcome this problem by developing a unique setup allowing single-use Rosemount pH sensors to be stored retracted and wetted within a chamber containing a stable, proprietary buffer delivering a two-year shelf life.

This configuration allows the sensor to be tested and calibrated while installed in the dry bag before being placed into production, at which time the sensor can be inserted for product contact. The buffer pH can be used as a calibration standard, and a one-point calibration at batch startup results in accuracy within 0.1 pH. Combined with the fact that the sensor has 0.005 pH per day stability, long runtimes up to 20 days are possible after insertion without any required recalibration or maintenance under most conditions. Additionally, one-point standardizations can be performed at any time against an offline sample to reset the sensor drift and continue the run. Thus, the sensors can be used for runs of any length.

Focus on DO

DO sensing methods are more forgiving than pH for single-use service. The DO sensor itself is the same as for classic SST processing applications and can be reused for multiple batches.

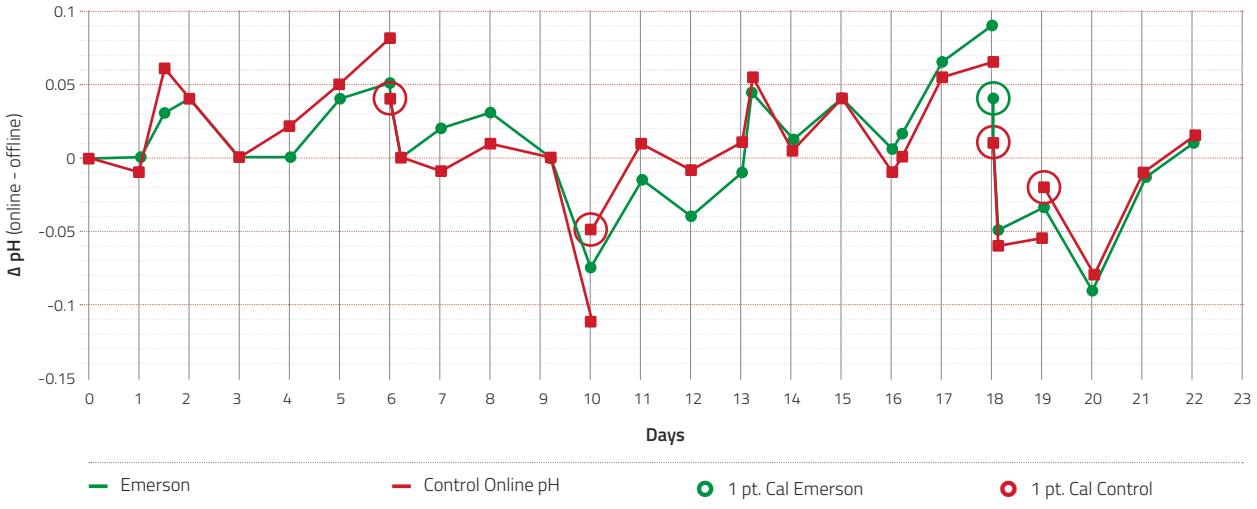


Single-use bioreactors offer numerous manufacturing advantages, but the instrumentation requires special attention to achieve performance equivalent to stainless steel systems.

EXHIBIT 1

Online pH drift against offline sampling

During testing in a 500-liter bag, Emerson's Rosemount single-use pH sensor compared favorably with online control measurements over a 23-day run, verified by offline sampling.



However, for single-use the DO sensor is installed in a fitting with a permeable oxygen membrane, so the sensor has no direct contact with the process media. While this does introduce a small lag time, it isn't an issue for this type of application where changes in DO occur relatively slowly.

If necessary, the DO sensor can be removed and calibrated on the bench, even during processing.

Single-use sensor applications

New single-use pH and DO sensors and fittings are designed for single-use bioreactors ranging in size from 10 to 4,000 liters. Because the sensors install into 1-inch barb fittings and are gamma irradiated with the bag, start-up is immediate.

These sensors can be employed in any application where a bag is used, not necessarily confined to only upstream fermentation and perfusion applications. With a large 2 to 12 pH sensing range, the pH sensor can also be used for in-bag applications involving viral inactivation, tangential flow filtration, and others.

In one test of the early pH prototypes in a 500-liter bag, Emerson's Rosemount sensor maintained stability much longer than the other online control sensor. Exhibit 1 shows the difference between the single-use online pH sensor and offline sampling measurements taken over this 23-day run. For this test, users triggered a one-point standardization if the online pH sensor deviated more than 0.05 pH from the offline measurement for two samples, or if the online sensor was ever more than 0.1 pH off from an offline measurement. The single-use sensor compared favorably to the control sensor, requiring only a single one-point standardization versus the four required for the control.

Finding the right answer

In many processing and manufacturing sectors, scaling up operations with large production equipment installations is the path to efficiency. Within the pharmaceutical industry, however, SST bioreactor installs are not always the right answer. Adopting SUT technologies like bioreactor bags minimizes the need for cleaning, sterilization and the associated expenses for WFI, chemicals, energy and supporting infrastructure. Single-use also offers newfound flexibility to scale operations up and down.

Since many of these processes are automated and all must be monitored, there remains a need for pH and DO instrumentation, which must use installation and calibration methods suitable for this demanding service. Updated instrumentation is now available to maintain the performance and familiar form factors of traditional instruments, but with enhancements to deliver long shelf life while meeting single-use sterility requirements.

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Meagan Parrish
Senior Editor

Advancing aseptic processing

How the industry's big ideas are impacting sterile manufacturing

While pharma has made tremendous strides in aseptic processing, the industry still struggles with contamination issues — indicating there is more work to be done. Like all segments of the pharma industry, aseptic manufacturing continues to be transformed by disruptive technologies. With the goals of maintaining compliance, lowering costs, and streamlining processes always at the top of mind for drugmakers, industry vendors are innovating solutions that incorporate the latest trends and capabilities.

"Firms are striving to reduce costs and improve process flexibility, while fundamentally eliminating some of the potential contamination challenges," says Ben Wylie, senior product manager at Charge-Point Technology.

Pharma may be close to mastering aseptic manufacturing, but innovative tweaks and updates to equipment and operations are helping improve the process even more.

Robotics

Robots have been a game-changer in the packaging department of facilities, and are now transforming the filling process as well.

"Robotics are progressively more available in aseptic processing due to the flexibility they allow — saving time for the operator who would otherwise need to change parts to fill very different kind of vials, syringes and cartridges," says Federico Fumagalli, chief commercial officer at Steriline. "With robotics machines, they just have to change a single parameter on the robot to change the whole production process."

Steriline's Robotic Vial Filling Machines are designed for campaign production with containment technology and feature vial transport with an anthropomorphic robot.

Steriline's Robotic Vial Filling Machine was designed specifically to address the industry's growing need for flexibility. According to the company, the machine can be equipped with one or two Stäubli vaporized H2O2 resistant anthropomorphic robotic arms (depending on output requirements), which transport the vials within the machine.

Although Fumagalli says there are pros and cons to using robotics, a cost-benefit analysis favors robots because they can reduce downtime, prevent product loss and decrease waste.

"In case a vial is not correctly stoppered, the robot can repeat the stoppering cycle to complete the process," he says. "On a traditional machine the vial would

be rejected — the content discarded — losing a potential earning, and the company would have to dispose of the waste, incurring further costs. Using a robotic system, the vial could go backwards and be stoppered during a second cycle, without any waste."

Fedegari Technologies has also been developing ways to combo advanced solutions, including robotics, into one piece of machinery.

"The manufacturing processes of the future will streamline new technologies like robotics, artificial intelligence and IoT, into an increasingly closed and connected production process," says Jeffrey Siterlet, managing director of Fedegari Technologies in North America. "By linking components, isolating the process and centralizing control, tomorrow's manufacturing process will facilitate efficiency, safety and compliance while eliminating risk."

The company's new washer sterilizer, for example, offers sterilization, washing and bio-decontamination in one solution. The gloveless sealed isolator hosts a GMP robotic arm that can be adapted for different batch sizes and simplifies cleaning requirements needed to enter a controlled-contamination environment.

Single-use

Single-use solutions continue to play a dominating role in pharma manufacturing innovations and provide a wide variety of benefits.

"As single-use and disposable products become more widely utilized, the manufacturing process becomes more efficient through quicker changeovers and set-up times and drug manufacturers can react more rapidly to product and customer demands," says Wylie.

ChargePoint recently added two products to its single-use portfolio including the ChargePoint Single Use Passive (SUP) and ChargeBag PE-S with new HiPure ULP7 PE film. Together, the two products are intended to form a high performance, single-use package for the contained and sterile transfer of powders between manufacturing process steps or even facilities.

The company says that the ChargePoint SUP is a disposable version of the passive mating half of the ChargePoint SBV (Split Butterfly Valve) technology, which forms a complete hybrid system to ensure users can take advantage of the benefits of disposable technology.

"Technologies such as SBVs are increasingly replacing traditional open transfer techniques, enabling contained and efficient materials transfers," Wylie says.

Importantly, single-use innovations are also happening for the final stage of the manufacturing process: Transport.

"As the trend of biologics being manufactured in one location and going through the final fill process in another grows, the need for materials that can withstand manipulation at temperatures down to -86 degrees C continues to accelerate," says Alex Kakad, product marketing manager for AdvantaPure.

AdvantaSil Ultra Low Temperature Silicone Tubing is designed to remain flexible (as opposed to cracking and leaking fluids) at temperatures as low as -112°C. According to the company, its tubing and molded closure assemblies have glass transition temperatures below -100 °C, allowing for a comfortable safety factor for these demanding applications. This, AdvantaPure says, makes the tubing an optimal choice for applications related to bulk drug storage and transport.

From the first stages of aseptic processing until products exit the factory doors, technology trends are continuing to transform sterile pharma operations.

Fedegari's new washer sterilizer features a cluster tool concept with a gloveless robotic isolator suitable for multiple formats and various batch sizes.

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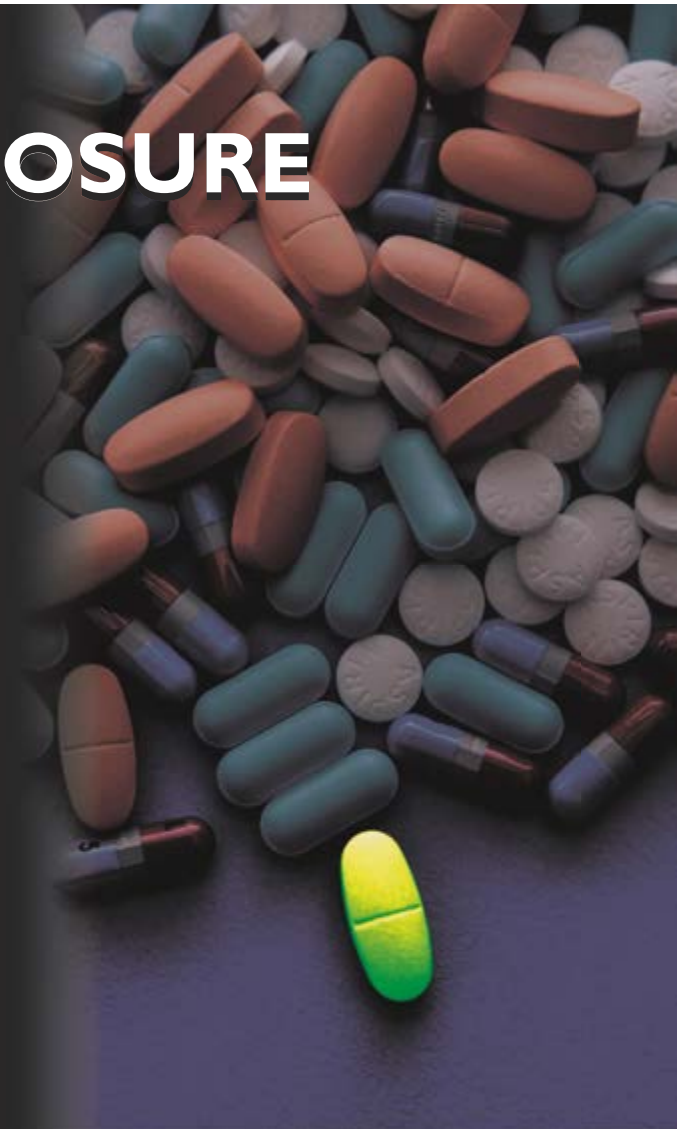

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Will product drift cause a rift?

It's important to consider how product drift will impact biosimilars

The U.S. is still in the nascent stages of biosimilars. In fact, the U.S. Food and Drug Administration (FDA) is so concerned about promoting biosimilars that they released a Biosimilars Action Plan (BAP) in July 2018 to better clarify how companies can obtain approval and to educate the public. With this, we've seen a significant increase of approvals, with nearly half (9 of 19) of the total biosimilar approvals in the U.S. coming in 2018 or 2019.

But with additional approvals, questions arise regarding manufacturing. Quality control can increase consistency, but it's challenging to ensure anything that comes from a living cell is exactly identical. Even minor changes in any component of manufacturing or quality control could lead to changes in the biologic product, which may ultimately impact the quality, safety, efficacy, or interchangeability of biologics. This change in the product and its characteristics that can occur over time as a result of manufacturing changes is referred to as "product drift."

As we continue to have multiple biosimilar and potential interchangeable approvals for the same reference product, it is important to consider how product drift will impact biosimilar products approved at different times, as well as the characteristics of the biosimilar product itself.

Biosimilar products approved under an abbreviated biologics license application (aBLA) pathway must be proven to be safe, pure, and potent for the approved use conditions. The proposed biosimilar establishes safety and effectiveness through a demonstration of biosimilarity to the reference product, and thus relies on the FDA's previous safety and effectiveness findings for the reference product. If product drift occurs, a reference product may have different characteristics over time, meaning that biosimilar products may actually be demonstrating biosimilarity to essentially different reference products depending on when they seek approval.

Although there's yet to be an approved interchangeable biosimilar in the U.S., the FDA provided draft guidance in early 2017. Interchangeable status requires, in part, a switching study that confirms the safety of alternating or switching treatment. This requirement could be complicated if the reference product exhibits product drift.

The FDA has asked for comments on how to address post-approval manufacturing changes of interchangeable products. Many stakeholders feel that current FDA regulation of post-approval manufacturing changes for reference products are sufficient, whereas others fear that biosimilar products may cease to be biosimilar and/or interchangeable with the reference product over time due to product drift, thus potentially requiring recurring testing.

The BAP lists one of its objectives as "providing additional support to product developers regarding product quality and manufacturing processes" — a clear opportunity to provide clarity on the issue of product drift impact. The FDA should address this issue now, particularly in the situation where an interchangeable biosimilar may seek approval several years after an initial biosimilar approval for the same reference product. If product drift is a legitimate occurrence, we may have a scenario where multiple biosimilar products are approved at different times, thus being interchangeable with the reference product (at different times), while not being interchangeable with each other.

Product drift in biologics has been traditionally managed through testing after any manufacturing changes and through post-marketing surveillance. Changes are tested against the batch used in clinical trials, so comparisons are always made back to what was initially approved. In fact, in the 35 years since biologics were approved, only three cases of product drift in 260 biopharmaceuticals in the U.S. and Europe were ever reported, and only one of those was proven to be a meaningful difference. But this lack of significant product drift may simply be product dependent, thus not ensuring that future products won't be impacted.

Perhaps product drifts concerns will not be significant as long as vigilance over manufacturing changes and post market surveillance remains. But it's impossible to tell at this early stage. Regardless of whether one believes that product drift will be a significant concern, the BAP provides an opportunity for the FDA and stakeholders to consider and discuss mechanisms for monitoring this issue to avoid potential patient impact. No matter how remote the possibility, the potential impact of product drift is simply too important to ignore.

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