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How drugmakers are fighting to keep reproductive health drugs available, safe and legal

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Karen Langhauser
Chief Content Director

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How drugmakers are fighting to keep reproductive health drugs available, safe and legal

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DEPARTMENTS

DIGITAL EDITION

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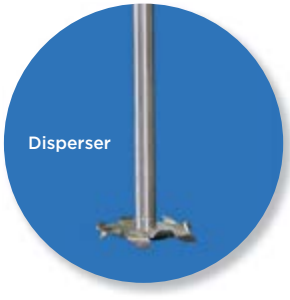

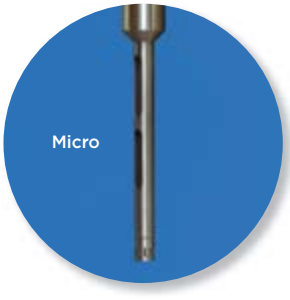

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Reproductive plights

The industry's mission to keep drugs accessible has become very visible

We need to talk about abortion — and there is no subtle way to start this conversation.

The discussion actually starts before the birth of Roe v. Wade, at a time when any contraception was considered 'lascivious' and 'immoral.'

In the early 20th century, oral contraceptives began battling their way through development, embroiled in religious and legal persecution. When the pill finally got approval for use as contraception, more than half of U.S. states still had anti-birth control laws on the books. It took two Supreme Court rulings, the second of which came 12 years post-FDA approval, to legalize birth control for all.

But surely as society evolved and we stopped viewing women as baby-making machines, the environment for reproductive health drugs became more hospitable, right? Consider that, in 2003, the manufacturer of the emergency contraceptive, Plan B One Step, submitted an application to the FDA seeking to switch the drug from prescription to OTC. The drug got tangled in regulatory delays, staff resignations, legal action against the FDA and political interference that went as high as the White House before finally getting full approval — ten years later.

Fortunately, along with their gritty histories, reproductive health drugs also have decades of documented safe and effective use. And generally speaking, drugs that have been on the market for 20+ years get a reprieve from controversy.

But as you will read in this month's cover story, it seems there is no rest for reproductive health drugs in post-Roe America. While the Dobbs v. Jackson ruling was viewed by many as the worst blow to reproductive rights in fifty years, it is quickly proving to be the harbinger of ongoing attacks. And on the industry side, drugmakers and the FDA are fending off blows.

With the power to regulate abortion shifted back to states, mifepristone, a medical abortion drug approved back in 2000, is currently bearing the brunt. There are only two drugmakers selling mifepristone on the U.S. market, and both are currently involved in high profile, high stakes lawsuits. Danco Labs, the brand owner, has joined the FDA in a Texas lawsuit that seeks to overturn the agency's approval of the drug nationwide.

Meanwhile, the generic drugmaker, GenBioPro, has gone on the offensive, suing West Virginia over its statewide abortion bans.

As the fate of abortion drugs plays out in the courts, pressure on the FDA and the rest of the reproductive health space to keep all drugs accessible is mounting. Last year, the FDA finally approved a request from the maker of Plan B to update the drug's label clarifying that it does not cause an abortion. In an effort to break down as many barriers to access as possible, two drugmakers are currently working with the FDA to bring their oral contraceptives over the counter.

While politicians paint abortion in black or white, for most people, reproductive freedom comes in many shades of grey. Throughout history, drugmakers navigating this space have always met with resistance, but the new legal instability created by the Dobbs ruling could have severe and reverberating consequences. Like many of you, I am watching the precarious situation unfold in real time. And with sorrow — for the millions of Americans who rely on these drugs for reproductive health — I dissent.

Karen Langhauser
Chief Content Director

The next chapter in cell and gene therapy

ATW 2023 celebrated a record-breaking year of approvals, with an eye on new realities

'Gottlieb mathematics' were recently trending in Miami.

Back in 2019, when Scott Gottlieb was heading up the Food and Drug Administration, he predicted that the agency would be approving 10-20 cell and gene therapies (CGT) per year by 2025. A lot of people had doubts.

When Kim Barnes, executive vice president for Phacilitate kicked off Advanced Therapies Week back in January, she commemorated 2022 as the year the commercial reality of CGT became apparent. In 2022, the U.S. saw a record-setting five CGT commercial approvals, including the first gene therapy authorized for hemophilia B.

The 2023 Advanced Therapies Week took place at the Miami Beach Convention Center from January 17-22 — and the vibe was both celebratory and future-focused.

It would seem that Gottlieb's somewhat aspirational math is on track to add up — which is good news for both patients and those dedicated to the advanced therapy space. But the excitement of new approvals is tempered with the reality of costs.

The problem of cost

Chairing the plenary, Anthony Davies, founder and chief executive officer of Dark Horse Consulting cut right to the chase, pointing out that many CGTs are "outrageously expensive" and "it's a problem."

"For the first time in history, we can make lifesaving therapies that we can't afford," said Davies.

When CSL Behring's Hemgenix became the first FDA-approved gene therapy for hemophilia B last November, the drug also set another record — price. The one-time treatment comes with a $3.5 million price tag — making it the most expensive drug in the world. While the price can be justified by the therapy's ability to decrease or even eliminate the need for regular injections of factor IX (patients with hemophilia B are typically given the protein once or twice a week to help blood to clot), the high upfront cost for payers is problematic.

With more gene therapies intended for conditions impacting larger patient groups such as

Top 10 CGT milestones from 2022

1. Limited patient access post approval
2. Approval second line large B cell lymphoma
3. First allogeneic T-cell approval
4. Leveraging trailblazers' prior experience and scale
5. Larger patient population growing pains
6. Big pharma dominates M&A
7. Hemophilia A and B drug approvals
8. Alternative funding
9. First gene therapy approval beyond rare disease
10. Big pharma expands toolkit

LIST COURTESY OF SUSAN NICHOLS, CHIEF BUSINESS OFFICER, VIROCELL BIOLOGICS

The U.S. FDA has approved 27 CGT products. By 2030, it is estimated that the FDA will have added 80 new CGT approvals.

— BioPharma Excellence

diabetes and heart failure cascading down drug pipelines, something must be done to address costs because current payment models in the U.S. can't support them.

"A great prescription if the patient can't fill it is meaningless," said Gwen Nichols, chief medical officer, Leukemia & Lymphoma Society.

Multipronged solutions

In order to realize "the most important next chapter in health care" it's going to take a "multipronged effort," from all stakeholders, said Steven Miller, chief clinical officer, Cigna Corporation.

First, the U.S. needs to put policies in place to stop wasting money, according to Miller. Perhaps one of the more shocking numbers shared during the event, Miller estimated that one-third of all health care spending in the U.S. is waste.

"There is enough money in the health care system to pay for cell and gene therapies, there's no doubt about it," said Miller. "If we can find that waste, get that waste out, that money can be reallocated for other things, like cell and gene therapies."

Insurance companies, for their part, are establishing risk pools to attempt to combine medical costs to calculate premiums for specific high-value medicines.

But perhaps most vital is the need for drug manufacturers to get production costs down as low as possible.

Several panelists throughout the ATW event pointed out that this cost-reduction starts in development. In order to engineer product to optimize manufacturing costs, CGT developers need to worry about robustness and reproducibility from the beginning, said Peter Zandstra, professor, University of British Columbia. This includes integrating novel technologies into the process to further enhance control of cell product identity, reproducibility and efficacy.

In a separate session focused on commercialization, Lung-I Cheng, vice president, Cell & Gene Therapy, AmerisourceBergen emphasized that CGT manufacturers should address commercialization functions in R&D discussions, designing and building for scalability.

"To ensure success many commercialization decisions need to be addressed early in the journey during the clinical stage," said Cheng.

Decisions should also be made with patients' best interests mind, stressed Cheng, advocating for a patient-centric approach to the treatment journey that is already very complex for patients.

By the end of Advanced Therapies Week 2023, it was clear that the industry has a lot of celebrate — despite all past and current obstacles, the age of advanced therapies has arrived.

Veronica Ghidotti
Product Manager, Visual Inspection Systems, Stevanato Group

A new way of looking at syringe inspection

How technology is rising to the challenge of inspecting prefilled syringes on the production line

Annual global drug spending has risen by $300 billion in the last five years to reach $1.3 trillion in 2022 — largely driven by biologics, which have seen a compound annual growth rate of 12%. The U.S. is the largest pharmaceutical market by value and its drug spending has continued to outgrow the global market — again, driven by biologics. Prefilled syringes specifically have flourished, growing by 19% according to IQVIA data.

Against this background, Pharma Manufacturing recently spoke to Veronica Ghidotti, Product Manager, Visual Inspection Systems at Stevanato Group, about the challenges of inspecting prefilled syringes on the production line — and how the company's new MAVIS automatic inspection platform is playing a vital role in streamlining inspection operations and reducing costs for pharma companies.

Q: What is driving the increased use of syringes to deliver drug formulations?

A: The increased use of syringes is part of the pharma industry's move towards simplified treatments for self-administration by patients. With chronic diseases such as diabetes and heart disease on the increase, the market for at-home self-administration drug delivery is rising. This has led to syringes becoming a popular choice for auto-injector devices.

Q: What are the advantages of prefilled syringes?

A: With a prefilled syringe, the process of administering a drug product can be safer, quicker and easier for health care workers and patients. Instead of having to prepare and draw the medicine into the needle, the correct amount is already present in the barrel, ready for injection. This reduces the risk of preparation and dosing errors and provides a more efficient drug delivery process.

Q: Why has syringe inspection been a historically difficult endeavor?

A: Syringes are arguably the most difficult containers to inspect, as they are delicate and require unique handling protocols. While other containers, such as vials and cartridges, largely 'stand still' and can therefore enter the inspection process independently, syringes typically have to be carried via a conveyor belt and then turned upside down. This is to ensure any particles hidden in the funnel sink into the liquid contents and can be detected.

> MAVIS automatic inspection platform is playing a vital role in streamlining inspection operations and reducing costs for pharma companies.

Another complication is that, if the syringes are sterilized, the containers are typically in a nest-and-tub arrangement, which means they have to be de-nested by a robotic unit communicating with the inspection machine. This requires gentle handling to avoid glass-to-glass contact to mitigate the risk of cracks or breakages.

The small diameters of syringes also present an inspection challenge because of the limited space in which particles can move and therefore be detected. This requires high-speed spinning so that any unwanted particles move toward the outside of the containers — this is especially important for turbid drugs. High-speed spinning also helps with the detection of bubbles — as bubbles go up while impurities go down.

Q: Are there limitations to the inspection techniques currently being used by drugmakers?

A: Inspection technologies range from manual and semi-automated through to fully automated, high-speed machines. When performing manual inspection, each syringe is inspected with fluorescent light against a black-and-white background. As manual systems remain subject to human error and do not offer the speed required for larger batches, they are mainly used for customized applications and stability surveys.

Semi-automated inspection systems can achieve more accuracy

MAVIS PLATFORM
Advanced inspection performances in a small footprint.

and reduce the need for manual handling. Automatic feeding, sorting and discharging functions enable inspectors to focus entirely on the quality control of prefilled syringes.

But the challenges outlined above remain — which is why Stevanato Group has created the MAVIS automatic inspection platform, which can handle drugs ranging from water-like solutions and suspensions to viscous or lyophilized products. MAVIS can inspect up to 400 pieces per hour — and all in a compact footprint that includes all the inspection stations to ensure top quality results.

Q: What are the benefits of deep learning applications in syringe inspection?

A: Deep learning technology uses neural networks to mimic the human brain's ability to learn by example. Once trained on thousands of images, deep learning algorithms enable an inspection system to identify patterns so that it can recognize defects in an item on the production line and distinguish particles from false positives such as bubbles.

The main benefits are enhanced accuracy and efficiency. Deep learning models improve over time and can detect a wide range of complex defects. They can help reduce the number of false rejects — and also the number of grey items that need to be re-inspected manually. So, the whole process becomes leaner, with less waste.

> Syringes are arguably the most difficult containers to inspect, as they are delicate and require unique handling protocols.

Q: What is different about the MAVIS automatic inspection platform?

A: MAVIS has independent motorized spindle rotation units that can be adjusted for different drug products. This ensures precise rotation of the syringes during an inspection, with no glass-to-glass contact. A smooth and stable transport system is provided by a servo-driven clip-wheel and belt continuous motion operation, with grippers available for Luer-lock syringes. A combination of matrix and line-scan cameras gives unrivaled inspection capabilities.

MAVIS has been designed to be user-friendly — the patent-pending visual interface requires no programming or scripting knowledge. And the de- and re-nesters are at the same end of the machine so that it can be run by one operator if required. It is also easy to install and maintain, and uses digital twin technology to enable the software configuration of the machine to be changed offline and validated during production — avoiding expensive downtime.

Q: What is coming next for the MAVIS platform?

A: In line with its clear focus on streamlining operations and reducing costs for pharma companies, Stevanato Group plans to launch a new machine as part of the MAVIS platform during 2023. It will enable the inspection of ampoules, vials and cartridges, as well as syringes. Instead of buying different units for different formats, pharma companies will be able to reduce costs by buying one single unit.

Karen Langhauser
Chief Content Director

nevertheless, they persisted

How drugmakers are fighting to keep reproductive health drugs available, safe and legal

It's a table at which most companies don't want to sit.

In modern day corporate America, companies are quick to belly up to certain causes — flying blue and yellow Ukrainian flags, blacking out social media in solidarity of racial justice, or switching to rainbow logos for Pride month. And yet, when it comes to reproductive rights, many companies don't seem to have much of an appetite for activism.

When the Supreme Court of the United States overturned Roe v. Wade last June, companies' long-standing silence got awkward. The pharma industry responded much the same way most businesses did — a handful of companies spoke up, with many somewhat skirting the issue by mentioning their own health care policies.

For most of the pharma industry, abortion is not a kitchen-table issue. Yet, for drugmakers focused on reproductive health, balancing drug manufacturing and reproductive justice is a familiar exercise. Even before the fall of Roe, drugmakers producing oral contraceptives, emergency contraceptives and medical abortion drugs have lived in a unique world of red tape, ideological opposition, stigma, misinformation and legal unease.

Samantha Miller, co-founder and co-chief executive officer at Cadence OTC, spent two decades working in the more traditional biopharma industry but says her foray into the reproductive health space was the first time she encountered this type of environment. "It definitely stretches companies beyond traditional activities into the political and advocacy realm," says Miller.

Now, the maelstrom effect of Dobbs v. Jackson has sucked in more than just access to abortion services. The decision has created confusion and chaos surrounding women's constitutional right to reproductive health. Currently, a Texas lawsuit seeking to overturn the Food and Drug Administration's approval of mifepristone, a medical abortion drug, is capturing media headlines. A lawsuit challenging state medical abortion bans, filed by a mifepristone manufacturer, is also underway in West Virginia. The outcomes of both lawsuits could have trickle-down effects that leak even further into the reproductive health drug space.

The need to secure access to all reproductive health drugs has become imperative — even for medications backed by decades of safety data. Against this backdrop of urgency, a handful of determined drugmakers are continuing to innovate ways to get safe, effective reproductive health drugs into the hands of people who need them.

Disunited states

Returning the power to regulate abortion to individual states has resulted in diverging reproductive health regulations — and drugmakers, as well as the FDA, are finding themselves caught in the middle.

According to attorney Skye Perryman, president and chief executive officer for Democracy Forward, a legal advocacy organization formed in the wake of the 2016 presidential election, while the effect of the Dobbs decision on women's rights is "incredibly concerning," it has also "emboldened a broad range of conduct that continues to be both harmful and unlawful, even in the wake of Dobbs."

Much of this conduct is playing out in the courts. Bearing the brunt of the legal fallout is the medical abortion drug, mifepristone. There are currently only two small drugmakers manufacturing mifepristone for the U.S. market: New York-based Danco Laboratories, which won approval for the branded drug, Mifeprex, in 2000, and Las Vegas-based GenBioPro, which got the nod for the generic tablets in 2019.

The FDA-backed protocol for medical abortion — which now accounts for more than half of U.S. abortions[1] — is to take two drugs in combination, mifepristone and misoprostol. While misoprostol can be used alone for medical abortions (the regime is supported by the World Health Organization and used internationally), in the U.S., misoprostol is only approved as a standalone treatment for gastric ulcers. Thus, removing mifepristone from the equation would complicate medical abortion in the U.S., forcing health care providers to use misoprostol off-label.

Back in January, GenBioPro, the generic drugmaker that controls the largest share of the U.S. mifepristone market, decided to go on the offensive. The company, which was launched in 2012 with the mission to bring generic mifepristone to market, filed a potentially landmark lawsuit alleging that the heavy restrictions that have been in place in West Virginia, combined with the criminal abortion ban enacted post-Roe, have halted access to mifepristone and the company's ability to do business in the state.

GenBioPro sells only two products — generic mifepristone and misoprostol. Sales from the two medical abortion drugs are the company's sole source of revenue.[2]

"In nine states with state abortion bans or no abortion clinics in operation, we have seen a 100% decline in sales," says a GenBioPro spokesperson.

In addition to the business case, the suit appeals to the company's founding principle of access advocacy.

"We are taking on this litigation because it is central to our mission of protecting access to reproductive health care. Since we brought our first product to market, we have been clear that protecting access to reproductive health care is a key priority of ours," says the GenBioPro spokesperson.

The West Virginia lawsuit is not the company's first dive into legal waters. Back in 2020, the drugmaker filed a lawsuit in Mississippi challenging statewide abortion restrictions, but voluntarily dropped the suit following the state's success in persuading the Supreme Court to overturn Roe v. Wade. At the time, GenBioPro indicated it would revive the suit elsewhere[3] — a promise the drugmaker appears to have delivered on in West Virginia.

"West Virginia is maintaining a series of laws and regulations that are in conflict with the federal

> **"Those of us in the field need to just stay tuned and keep pushing because none of the gains we have had in the past 50-100 years have come easily."**
>
> — Nap Hosang

Notable regulatory events in reproductive health

JUNE 1957
FDA approves G.D. Searle's Enovid as a treatment for menstrual disorders and infertility

JUNE 1960
FDA approves Enovid as the first oral contraceptive

DECEMBER 1988
FDA approves G.D. Searle's Cytotec (misoprostol) only for the prevention of gastric ulcers associated with the use of NSAID drugs

JULY 1999
FDA approves Women's Capital Corp.'s Plan B for use as emergency contraception

SEPTEMBER 2000
FDA approves Danco Labs' Mifeprex for medical termination of pregnancy through seven weeks gestation (extended to 10 weeks gestation in 2016)

AUGUST 2006
FDA approves Rx-to-OTC switch for Plan B One Step emergency contraception (now owned by Barr Pharmaceuticals) for consumers age 18+

JUNE 2011
FDA establishes a risk evaluation and mitigation strategy (REMS) program for Mifeprex

JUNE 2013
FDA approves Rx-to-OTC switch for Plan B One Step (now owned by Teva Pharmaceuticals) with no age restrictions

AUGUST 2019
FDA approves GenBioPro's generic version of Mifeprex, mifepristone tablets

DECEMBER 2022
FDA approves label changes to clarify that Plan B One Step (now owned by Foundation Consumer Healthcare) works by preventing ovulation and does not cause abortion

JANUARY 2023
FDA updates mifepristone REMS requirements, permanently removing the in-person dispensing requirement and adding a pharmacy certification process

regulatory structure," says Perryman, who is part of the robust legal team representing GenBioPro. "We know the harmful impact that has on mifepristone access and it's unlawful. But you can imagine the broader implications of this as well."

As the mifepristone legal battles unfold, exactly how broadly their implications reach within the reproductive health drug space will become more apparent.

Standing with safety

With the ink barely dry on Dobbs v. Jackson, a Trump-appointed federal judge in Texas holds the pen on what will likely be the next high profile ruling on abortion. Last November, four anti-abortion medical associations represented by Alliance Defending Freedom, a conservative Christian legal group, filed a lawsuit challenging the FDA's approval of mifepristone. The Alliance for Hippocratic Medicine v. FDA suit contends that the agency approved the drug without proof of safety under the labeled use conditions and then continued to disregard its safety issues.

In mid-January, Danco Labs, a little-known company that, by design tends to fly under the radar, filed a motion to intervene, joining the defense in the ongoing lawsuit. In a press release, Danco, whose sole marketed product is Mifeprex, noted its concerns about a judge blocking the availability of the drug nationwide as well as a weightier issue — the "direct challenge to the FDA approval process for all pharmaceutical products."[4]

The case has incited a flurry of legal speculation — as well as panicked headlines — regarding the broader consequences of challenging FDA approvals. *First mifepristone, then what?*

The FDA, for its part, is standing by mifepristone's robust, evidence-based approval — a review process that took the agency

close to five years to complete. In the event that court proceedings force the agency to start the congressionally mandated process to re-review the drug, 23 years of safety and efficacy data should ultimately prevail.

In fact, some argue that the FDA regulation of mifepristone's safety risks is too strict — and that it's hampering access to the drug. Mifeprex and generic mifepristone are available under the FDA's rare risk evaluation and mitigation strategy (REMS). Established in 2007, REMS programs are put in place for certain medications with serious safety concerns to help ensure the benefits outweigh the risks. Out of more than 20,000 FDA-approved drug products, there are only 61 individual and shared REMS programs.[5]

Early in the pandemic, the FDA relaxed the in-person dispensing requirement in mifepristone's REMS, allowing the drugs to be dispensed by mail. In January 2021, the Supreme Court granted a Trump Administration request to reinstate the in-person requirements. Later that year, the FDA began a review of the REMS program, asking both drugmakers to submit updated prescribing information and REMS materials. The updates were approved by the FDA and went into effect on January 3, 2023.

The updates allow for mifepristone to be dispensed by mail and in retail pharmacies, however the pharmacies must be specially certified and execute the required 'pharmacy agreement form' with either Danco Labs or GenBioPro.

While this decision was heralded as a win for abortion drug access, some, including a dozen Democratic-controlled states, think it doesn't go far enough. The states are now also suing the FDA, seeking that the agency remove the mifepristone REMS entirely. The suit, filed in a federal district court in Washington state in late February,

Notable legal actions in reproductive health

MARCH 1873
Congress passes the Comstock Act, an anti-obscenity act that bans the dissemination of "any article of an immoral nature, or any drug or medicine, or any article whatever" for the prevention of contraception or procuring of abortion through the U.S. mail or across state lines

JUNE 1965
U.S. Supreme Court ruling in Griswold v. Connecticut legalizes birth control for married couples

MARCH 1972
U.S. Supreme Court ruling in Eisenstadt v. Baird legalizes birth control for unmarried people

JANUARY 1973
U.S. Supreme Court ruling in Roe v. Wade establishes that the right to privacy implied in the 14th Amendment protects abortion during the first trimester of pregnancy as a fundamental right

JUNE 1992
U.S. Supreme Court ruling in Planned Parenthood v. Casey affirms the basic ruling of Roe v. Wade that the state is prohibited from banning most abortions but upheld a number of Pennsylvania abortion requirements cited in the case, while broadening the authority of states to regulate abortions

JANUARY 2021
U.S. Supreme Court ruling in FDA v. American College of Obstetricians and Gynecologists reinstates long-standing restrictions for patients seeking to obtain mifepristone

JUNE 2022
U.S. Supreme Court ruling in Dobbs v. Jackson Women's Health Organization overturns the precedent set by Roe v. Wade affirming the constitutional right to abortion

> **Since its approval, mifepristone has been used over four million times. Medical abortion now accounts for 53% of all U.S. abortions.**
>
> — Guttmacher Institute

points to decades of safety data, questioning why mifepristone is put in the same category as dangerous and addictive opioids like fentanyl.

The states' suit does not mention the Texas case specifically, however the states are asking that the court declare that "mifepristone is safe and effective" and that the FDA's approval of mifepristone is "lawful and valid." The plaintiffs are also asking the court to prevent the FDA from "taking action to remove mifepristone from the market or reduce its availability."[6]

The 1938 Federal Food, Drug and Cosmetic Act granted FDA sole authority to regulate drugs, so many FDA law scholars assert that there is no judicial 'magic wand' that can wipe mifepristone — or any approved drug — from the market. The reverse should also hold true; a judge can't force the agency to keep a drug on the market.

Ultimately, mifepristone's market fate comes down to safety — a case that both Danco Labs and GenBioPro are confident they have the data to make.

Born into controversy

A lesser-discussed concern lurking in the depths of Dobbs and mifepristone litigation is that states could plunge further into the reproductive health space and seek out ways to restrict access to birth control.

The right to contraceptives was first recognized by the Supreme Court in 1965, and since then, attempts to codify that right into law — such as the Right to Contraception Act — have failed along party lines.

But in the oral contraceptives space, access barriers are nothing

new and were initially so pronounced that drugmakers had little interest in bringing a birth control pill to market.

'The pill' was born into religious opposition and an inhospitable legislative environment. It wasn't until 1957, when drugmaker G.D. Searle won FDA approval for a drug that combined progesterone and estrogen — as a treatment for menstrual disorders — that the business case was realized. By 1959, half a million American women were being prescribed the drug, branded Enovid, presumably *not* for menstrual disorders.[7]

Three years later, the FDA approved Enovid as the world's first commercial oral contraceptive — but the drug regulator's decision clashed with existing state laws. More than half of U.S. states had anti-birth control laws on the books, restricting contraceptives. One of the strictest, Connecticut's Barnum Act, banned information, advertisement or sale of any type of birth control.[7]

It took a deliberate act of civil disobedience by the executive director of the Planned Parenthood League of Connecticut, Estelle Griswold, and a Supreme Court ruling (Griswold v. Connecticut, 1965) to legalize birth control for married couples. A second Supreme Court ruling (Eisenstadt v. Baird, 1972) was necessary to extend that right to unmarried people.

Despite the state-level controversy over birth control, the market for oral contraceptives flourished. By 1970, seven different pharma companies had received FDA approvals for birth control pills and 13 major drug companies were actively pursuing birth control research and development.[8] By the early 1980s, 10.7 million American women were taking oral contraceptives.[7]

Planning for the future

While no state has sought an outright ban of oral contraceptives in modern times, state policies can both enable and restrict access to contraceptive care.

In 2017, Iowa opted to leave the federal Medicaid family planning program and establish its own state-run program that would exclude any clinics associated with abortion from funding. Unfortunately, many women were relying on these clinics for access to oral contraceptives. A Guttmacher Institute study found that the Iowa policy changes, driven by anti-abortion ideology, led to serious disruptions in access to affordable contraceptives.[9]

The federal Medicaid statute does classify family planning as mandatory, and overall this has made oral contraceptives more available to those who qualify. However, there are still many Americans who struggle with access.

"The bigger issue is people who are uninsured," says Nap Hosang, co-founder, co-chief executive officer and chief medical officer for Cadence OTC. "It's the people who are in between — not low income enough to be on Medicaid but do not have access to insurance."

A 2022 Kaiser Family Foundation Women's Health survey reported that one in five uninsured females of reproductive age had to stop using a contraceptive method because they couldn't afford it.[10]

A disturbing statistic lends credence to the persistence of access barriers: Despite a plethora of safe and legal contraceptive options, unintended pregnancies in the U.S. are hovering at around 50%.[11] The desire to solve this issue prompted a group of reproductive health experts and pharma leaders to come together in 2016 and take action, launching Cadence OTC.

"Unintended pregnancy was public health issue that needed major attention in the United States," says Hosang. "We needed to do something about accessibility of the birth control pill."

Formed with the mission to bring oral contraceptives over the counter, Cadence OTC is a small California-based, public benefit company (PBC) — a unique legal designation in the pharma space. PBCs essentially have a double bottom line in their company charters, meaning the company must make business decisions geared towards generating both profits and positive social impact. Cadence has spent the last seven years working to deliver on this dual promise.

Freeing the pill

In order to initiate the first-in-class Rx-to-OTC switch, Cadence had to first acquire the rights to a branded drug.

"There are only a small number of NDA [New Drug Application] owners in the world for regular combined oral contraceptives," explains Miller. "And the drug needed to be the mainstream dosage and we wanted it to be the progestin molecules that are considered the safest in the class, which is levonorgestrel." Miller's first mission at Cadence was to find this NDA needle in the predominantly generic drug haystack.

In 2018, Cadence bought the rights to two estrogen-progesterone

Oral contraceptives are the most popular nonpermanent method of birth control in the U.S.

— Centers for Disease Control and Prevention

combo oral contraceptives, Lo/Ovral and Alesse, from Pfizer. Pfizer had picked up the pair as part of its 2009 takeover of Wyeth-Ayerst Laboratories.

NDAs in hand, Cadence set out on the long road towards OTC approval for the drug it has branded as Zena. The company is currently focused on consumer label pivotal studies.

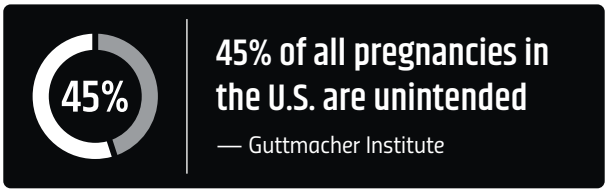
"Label development involves taking the physician package insert and communicating all of that information in a way that consumers can understand — and not only the average consumer, but adolescent consumers and low literacy consumers," says Miller. "It's a long, extensive process because you're constantly developing the label, testing it with consumers, changing it and testing it again."

Following the fall of Roe v. Wade, 12 U.S. states have near-total bans on abortion. This number could reach 24 depending on the outcome of lawsuits.

— Guttmacher Institute

Cadence has been collaborating closely with the FDA to develop a technology-assisted label under the agency's new additional condition of nonprescription use (ACNU) program. The proposed ACNU rule, released by the agency in June 2022, makes it clear that the FDA is willing to accept new ways for consumers to appropriately use drug products without the supervision of a health care practitioner.

Because certain groups of women — such as smokers over age 35 or those with uncontrolled high blood pressure — have an increased risk of serious complications from oral contraceptives, an OTC label must enable consumers to self-select for such conditions. Cadence's label uses a QR code to get to a web-based health questionnaire that asks consumers health-related questions to determine whether the product



is right for them or whether they should speak with a physician first.

Once the label is developed and tested, Cadence can move on to the final step, the actual use trial, during which the company will test Zena's use in a real-world setting. The pot of gold at the end of the actual use trial, should the drug get approved for the switch, is a three-year period of exclusivity.

Cadence started the regulatory process long before the fall of Roe, but the current climate has added new meaning to the mission.

"Cadence is under more pressure to move quickly and we are receiving more support as well," says Miller. "So we are more determined than ever despite the many impediments on the path."

Pushing oral contraceptives over the counter has the endorsement of major medical associations, policymakers, and high-profile advocacy groups. The country may have an answer soon too — while Cadence has not yet submitted its application to the FDA, Paris-based HRA Pharma filed to switch its progestin-only birth control pill with the agency last summer.

If history is any indicator, the mission to bring a reproductive health drug over pharmacy counters is not for the faint of heart. The sector's only example is the emergency contraceptive drug, Plan B, which took ten years to go from prescription to OTC. Susan Wood, who resigned her position as head of the FDA's Office of Women's Health because of the Plan B regulatory delays, later referred to the unfoldings as a "tortuous, and indeed politicized, process of approving a safe and effective, but time-sensitive, contraceptive product for over-the-counter sale."[12]

Undeterred by cautionary anecdotes, Cadence — per the company's mission — remains focused on knocking down obstacles between women and reproductive health options.

"Part of being part of this movement involves recognizing that we need to pay attention to not only the social consequences of lack of access, but also to the rights of all people seeking contraception," says Hosang.

Joined in dissent

The acute pain of the Dobbs v. Jackson decision has slowly given way to chronic aches throughout the reproductive health drug space. Drugmakers looking to bring new drugs to market — or keep old drugs on the market — face a disparate landscape of laws and beliefs.

While roadblocks are part and parcel for the reproductive health space, drugmakers continue to find ways to keep drugs accessible. And they have decades of safety data — plus the collective voices of millions of advocates — fighting on their side.

"Those of us in the field need to just stay tuned and keep pushing because none of the gains we have had in the past 50-100 years have come easily. For us to make substantial gains going forward, those who are committed need to just keep pressing ahead," says Hosang.

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Laércio Fernandes
Product Marketing Manager, Thermo Fisher Scientific

Ensuring business continuity in the lab

How modern chromatography data systems can help mitigate disruption

As pharmaceutical manufacturing increasingly moves to 24/7 operation, any interruptions have the potential to be extremely costly, both financially and in terms of reputational damage. All supporting services — which include pharma laboratories providing critical analytical data — must also operate round-the-clock and take steps to ensure continuous delivery.

Many different internal and external events can impact the ability of a business to operate continuously, from local power outages to global supply chain problems. However, in today's highly connected industrial environment, there is particular concern with maintaining the continuity of digital systems and protecting valuable data. The growing incidence of cyberattacks poses a significant threat to the pharma industry, which in recent years has seen an increase in the number of companies dealing with the damaging consequences of such events.

Key in mitigating the risk of interruption is the development of a business continuity plan (BCP) within which laboratory data systems must be protected against the consequences of any adverse events. The choice of systems installed in a lab affects the ability to maintain uninterrupted operation and safeguard data — and having the right hardware and software helps deliver greater resilience. Modern chromatography data systems (CDS) are equipped with intelligent tools that provide the flexibility, scalability and robustness required to ensure the security of laboratory data and support business continuity.

The BCP process

Maintaining productivity in the face of unforeseen circumstances is challenging. Businesses are prone to interruptions that range from minor to catastrophic. Modern laboratories are highly infrastructure-dependent, and their operation is predicated on access to complex support services, including sophisticated IT systems.

Business continuity planning is crucial for mitigating the risks of interruptions. The BCP process helps companies develop a system for prevention of, and recovery from, potential threats to the company (Exhibit 1). The BCP ensures personnel and assets are protected and can function quickly in the event of an incident. It identifies all risks that can affect operations, from natural disasters to human-made events, such as cyberattacks.

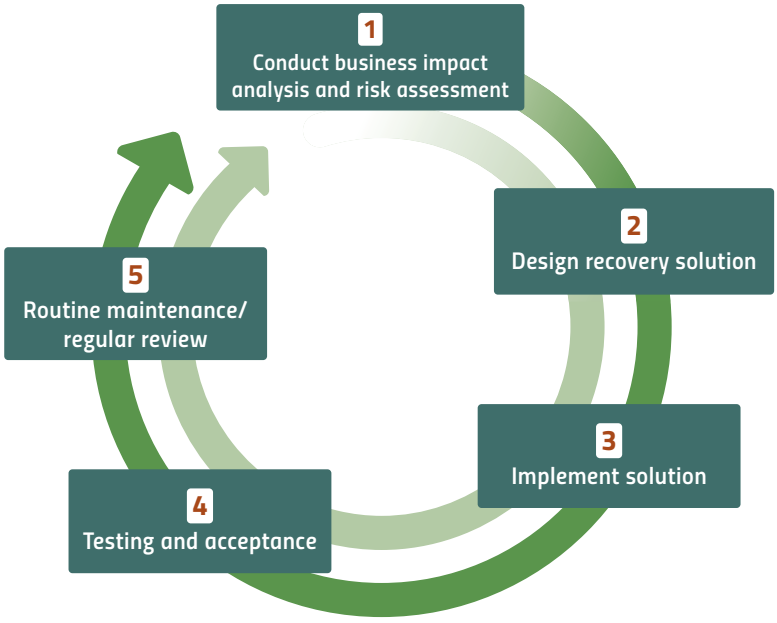
The business continuity planning process begins with conducting a risk assessment for all potential threats and their impact on the laboratory and the business. The second stage is to design a recovery solution that gets the business back up and running quickly, and the third is to implement the solution. Next, it is critically important to fully test the solution, make sure it works in practice, and then accept it.

Finally, regular maintenance and review is essential to make sure that the plan keeps up with a changing operating environment and takes account of new and evolving threats. The outcome is a plan that defines how risks will affect operations; the safeguards and procedures intended to mitigate those risks; the testing procedures in place to make sure they work; and the review process that ensures the plan is up to date. Communicating the plan effectively across the business is vital and sometimes overlooked.

A key part of any BCP is a disaster recovery plan (DRP). This is aimed at IT infrastructure and how to get it back up and running if things go wrong. Unlike the BCP, which is proactive and designed to identify and mitigate risks across the whole business, the DRP is reactive. It is designed to restore operations and outlines the steps needed to restart, reconfigure and recover systems and networks, and it includes data backup and restore. In the laboratory, choosing data systems that are designed to comply with zero-loss data security and continuous operation contributes to the resilience of both laboratory operations and the business overall.

EXHIBIT 1

Business continuity planning process



Picking the right CDS

Within the pharma laboratory, chromatography-based and mass spectrometry-based analytics are fundamental to both development and manufacturing operations. This makes the choice of a chromatography data system (CDS) critically important, with an emphasis on a resilient architecture that offers the flexibility, scalability and robustness needed for both data security and business continuity. The software should also provide protection from unplanned downtime and safeguard against cyberattacks.

So, what are the key CDS capabilities for business continuity? Examining the various risks and the questions they raise helps illustrate what makes for a good CDS:

Power outage

What if servers go offline? What happens to the data in a full power outage, and what happens when the power comes back on?

Depending on where the power outage occurs, the CDS can help in different ways. A full power outage in the lab will mean that no instruments or computers are working. However, what is important is that the data from any applications running at the time is secured. If power goes off elsewhere in the building, and the local instrument controller PCs lose connection to the main server, an innovative CDS will help access data locally and keep the lab running. When power is restored, the CDS should automatically reconnect the instruments to the network and upload data.

Network failure

Network failure is arguably the most common issue labs face. So, what happens to data that was acquiring, how can data be accessed, and is it possible to start new acquisitions?

Again, the primary concern is to secure the data. Whatever was running must be stored and not lost. In a regulated environment all the data must remain compliant with data integrity maintained at all times.

An advanced CDS will ensure that the network-based resources required to properly operate the software, such as license information and user management data, are automatically cached on local instrument controllers and computers, so that operation can continue. If the network is down, the local instrument controller PCs will continue the analysis without interrupting data acquisition. This enables access to the data for processing and reporting and allows initiation of new sequences, all in accordance with compliance and data integrity guidelines.

Ideally, in the event of network failure, the CDS will enable a specified recovery period to allow sufficient time for resolution of the issue or implementation of a longer-term solution. Furthermore, switching to network failure mode should happen automatically and immediately without any manual intervention. Upon restoration of the network, the CDS must have the capability to upload the interrupted data, complete with audit trails from within the software because any data export and backup may have data integrity implications.

A key part of any business continuity plan is a disaster recovery plan.

Third-party service provider outage

A recent data industry survey found that third-party services are uncommon sources of outages since the security offered by cloud service providers includes measures to prevent system failure and ensure continued access to services (Exhibit 2).[1] However, they can occur, and this raises the question of whether or not it is possible to have a mixed setup that allows onsite as well as third-party data storage.

The key goal is to keep the lab running — so a CDS that enables the use of local and regional as well as global data centers increases system performance and reliability. As with network failure, in the event of cloud provider outage the CDS needs to operate using local systems that enable user logon, license availability, data access and the ability to acquire new data, all within the framework of data compliance and integrity.

Human error

Human error is a significant factor in operational failures, so increasing the levels of automation and reducing the need for personnel interactions with data systems is highly desirable.

IT departments have requirements to apply controls to operating systems and ensure appropriate user restrictions are in place. The CDS too must have a user management system that can either be linked to wider systems or sit as a separate operation. A CDS with a separate login allows controlled data access and provides an extra layer of security. Being able to roll out and update systems centrally from a remote position is also important and ensures all such processes take place in a controlled manner.

Within the CDS, increased automation ensures users carry out tasks in a consistent fashion and follow standard operating procedures. This means having a streamlined way of creating a sequence, and as much automation as possible around data processing. Being able to put all calculations into a validated and integrated reporting engine is also important, ensuring that everything is backed up and avoiding the use of uncontrolled tools, such as Excel, in the laboratory.

A modern CDS is equipped with intelligent tools that provide the flexibility, scalability and robustness required to ensure the security of laboratory data.

Software or hardware failure

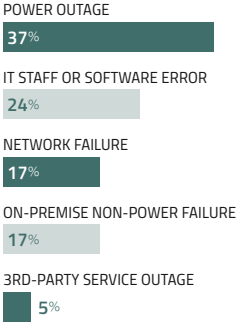
Can the CDS help to automate switchover to another IT resource, and does it help with the robustness of the system?

While load balancing (the sharing of workload between two or more servers) and failover (automated switching between servers if one fails) is often handled by IT teams, there are benefits to having a CDS that provides its own local systems. Built-in load balancing and failover, when configured, increase the

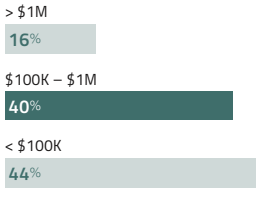
EXHIBIT 2

Information technology system concerns

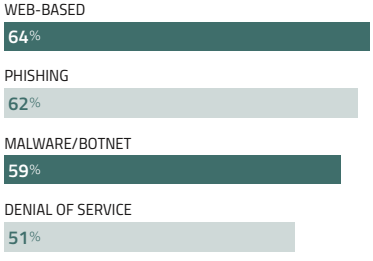
Cause of outages



Cost of outages



Business cyberattacks



Outages experienced

- **78**% at own or service provider site in last 3 years
- **31**% 'significant, serious or severe' event in last 3 years
- **75**% most recent outage could have been avoided

Cost of outages

- Cost is rising with **56**% costing over $100,000
- **98**% say one hour of downtime costs over $100,000

Cyberattacks

- **57**% of attacks target medium/large business
- Pharma industry malware and ransomware attacks increased **150**% from 2018 to 2019
- Average cost $4 million per year

SOURCES: UPTIME INSTITUTE EIGHTH ANNUAL DATA CENTER INDUSTRY SURVEY REPORT, CYBINT 15 ALARMING CYBER SECURITY FACTS AND STATES

performance, reliability and robustness of the data system.

If failure does occur, then it must be possible to rapidly restore the system. Consistent, automated backup ensures that the CDS can be restored quickly without data loss. A service-level agreement with the CDS provider is crucial to ensure both fast support from the manufacturer and access to their wider knowledge base and issue resolution.

Unauthorized access and cyberattack

Whether it is accidental or purposeful, unauthorized access to data and software risks severe damage to the system and may result in inoperable software, data corruption or even data loss. To prevent this, controlled access is critically important, with multiple security layers offering the necessary protection.

Equally important is the architecture of the software, which should ideally separate administration and data management. This concept allows functional separation to minimize risk, improve system reliability and facilitate security. It enables central administration to be achieved, which helps remove bottlenecks from usage, improve efficiency and maintain greater system control.

In modern innovative software, data storage is managed through a dedicated Data Vault service that connects the database and file storage. Access is routed through this service to provide a high level of robustness, security and scalability. Secure encryption of all communications — data in transit or storage — ensures the highest network security and data integrity. Since the management system provided by the CDS maintains access control, users can only perform actions designated by their logon role. Data cannot be intercepted or lost, productivity can be maintained and there is less vulnerability to cyberattack.

Ensuring streamlined operations

Pharmaceutical laboratories are under increasing pressure to ensure 24/7 operations, and as more data is digitized there is particular concern over maintaining the continuity of digital systems and protecting valuable data. Business continuity planning and implementation is essential to mitigate this and must take account of all possible threats to operations and the impact each is likely to have. Laboratory data systems play a significant role in data security and in supporting business continuity, and when making selections it pays to examine exactly what an advanced CDS has to offer.

A modern CDS is equipped with intelligent tools that provide the flexibility, scalability and robustness required to ensure the security of laboratory data and support business continuity. The choice of system can positively affect a lab's ability to plan successfully for unforeseen events and maintain 24/7 laboratory operation. To perform effectively, the CDS must meet the needs of both the laboratory and IT teams. It must deliver a solution that minimizes and protects against system outages and malicious attacks. And it has to enable uninterrupted access to data and instruments. Ultimately, making the right choice of CDS is a critical step in building robust operations.

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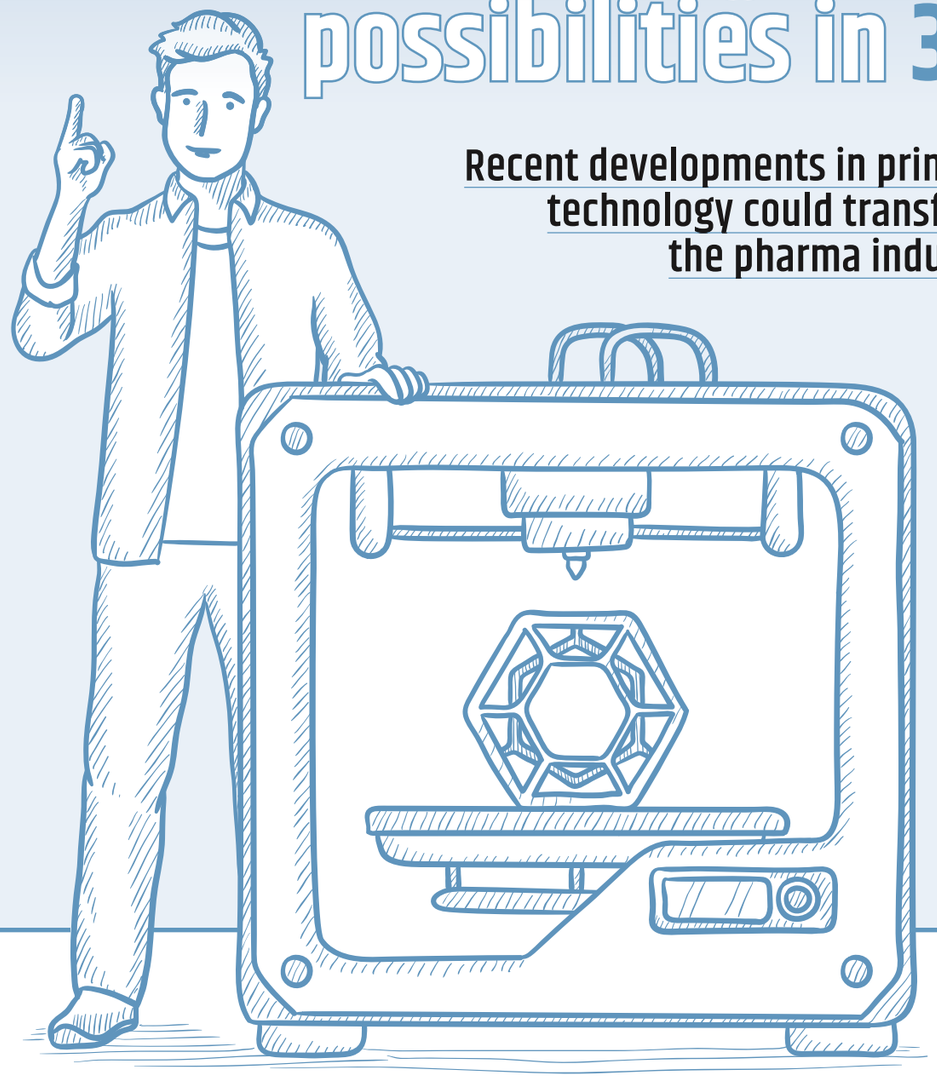
Prachi Khamkar
Research Scholar, Pharmaceutical 3D Printing
Founder, Atlaas Pharmaceutical

Unlocking novel possibilities in 3D

Recent developments in printing technology could transform the pharma industry



Three-dimensional (3D) printing technology, also known as additive manufacturing, is highly innovative and has the potential to be widely used across many different fields. The technology offers enormous possibilities for pharmaceutical production, from providing personalized medication to speeding up the drug discovery process.

3D technology provides options for altering pill shapes, dosing flexibility, improving solubility, and producing many tablets with various active medicinal components. Delivering customized, tiny batches in the clinical trials sector has immense potential. 3D-printed tablets, which may be made on demand in local health care settings, could help usher in a new era of individualized treatment in the field of patient-centered medicine.

3D technology has been rapidly growing in popularity, and it is expected to bring about significant changes in the way medical care is provided, particularly in the manufacturing of personalized medicine. However, in order to grasp this new universe of opportunity, a greater comprehension of the materials, processes and techniques will be required.

Personalized medicine

Personalized medicine involves creating medication tailored to individual patients based on their unique physiology, drug response and genetic profile. Several technologies are emerging to help the industry move away from the traditional 'one-size-fits-all' approach towards personalized medicine, with 3D printing being the most significant.

3D printing involves creating a three-dimensional object layer by layer using computer software. It has the ability to construct various pharmaceutical dosage forms with different shapes, release profiles and drug combinations. Recently, the technology became more complex, allowing different drugs to be combined in one tablet with different release profiles tailored to a patient's needs.

Intradermal drug delivery

The delivery of medications into skin layers in a minimally invasive manner is called intradermal (ID) drug delivery. These treatments usually focus on the epidermal or dermal layers that are above the nerve fibers and blood vessels of the skin. Compared to intravenous injection, ID drug delivery is a preferable choice as it can provide targeted, local drug delivery without causing systemic effects. One of the main benefits of ID drug delivery is its ability to administer compounds that have a significant first-pass effect or undergo metabolization by the liver.[1]

The ID space has been investigated as a way to deliver drugs and perform diagnostics with minimal invasiveness. Microneedles, microneedle patches and microarray patches (MAPs) use tiny projections that can painlessly penetrate the skin to access the epidermal/dermal layer. Surprisingly, MAPs have not reached their full potential due to outdated manufacturing processes that limit the variety of MAP geometries and scalability.

However, 3D printing can transform MAP development and create new opportunities for minimally invasive drug delivery and diagnostic platforms. The DeSimone Laboratory at the Massachusetts Institute of Technology has developed a new 3D printing technology called continuous liquid interface production (CLIP) that uses light and oxygen to create a polymerization dead zone, enabling the rapid production of MAPs with precise geometries. This technology has allowed for the production of new classes of lattice MAPs (L-MAPs) and dynamic MAPs (D-MAPs) that can deliver both solid and liquid cargos and sample interstitial fluid.

Drug-loaded implants

Fused deposition molding (FDM) can be used to create highly complex drug delivery implants that are personalized to meet individual patient needs. However, the activity of the drug requires specific processing temperatures and preparation methods for filaments, and the materials used for the implant must meet strict biocompatibility requirements.

A recent study sought to use FDM printing to develop a drug delivery implant that exhibited good biocompatibility and efficient and controlled drug release. Drug-loaded filaments were prepared for FDM using hot-melt extrusion (HME), with polycaprolactone serving as the drug delivery carrier and ibuprofen as the model drug. Controlled and efficient release channels were formed by dissolving chitosan.[2]

The study investigated the printability of the filament, changes in physical and chemical properties during HME and FDM processes, drug release behavior, mechanism and biocompatibility of the implants. The results demonstrated that the filament's tensile strength decreased as the drug and chitosan content increased, but there were no significant degradation or chemical changes observed during the process. The drug release efficiency exceeded 99%, lasting for 120 hours primarily via the diffusion-erosion mechanism. Cell viability was 75.3% after 24 hours of culture.

3D technology is expected to bring about significant changes in the way medical care is provided, particularly in the manufacturing of personalized medicine.

3D technology will help the industry to shift away from the conventional methods used for the mass manufacture of medications.

Colon drug delivery

A set of chronic, incapacitating inflammatory illnesses that affect multiple organs of the gastrointestinal (GI) tract collectively make up inflammatory bowel disease (IBD). From the beginning of the twenty-first century, the incidence and prevalence of these diseases has increased globally, and this trend is anticipated to continue. The effectiveness of a commercial formulation that works for everyone with IBD is still restricted due to the complicated and diverse clinical presentation seen in various individuals.

In Singapore, scientists created the dosage form of budesonide, a novel adjustable and controllable release 3D-printed colonic-targeting drug, to minimize unintended side effects and perhaps replace the usage of enemas, which are intrusive and frequently linked to poor adherence.[3] The study tested the capacity of the 3D-printed tablets to transport budesonide to several targeted areas along the gastrointestinal tract using an in vitro Gastrointestinal Simulation System (GISS) model.

The association between the 3D-printed design and subsequent disintegration profiles was developed for tablets with pill-in-pill combinations. Also, the quality and precision of the dosage was excellent and equivalent to those of conventional tablets, and the 3D-printed tablets improved the transport of budesonide to the targeted colon area. Ultimately, the work has established the fundamental proof of concept showing controlled targeting of oral medicines along the GI tract utilizing 3D printing technology.

Medicated lens

The invention of 3D-printed lenses can successfully address the disadvantages of existing techniques by employing biocompatible medical grade polymers that offer continuous medication release of timolol maleate over extended periods of time. A group of international researchers recently set out to develop 3D printing technology for the design and manufacture of drug-eluting contact lenses (DECL) for glaucoma therapy.[4]

Hot melt extrusion and fusion deposition modeling were used to create printable filaments using blends of ethylene-vinyl acetate copolymer and polylactic acid that were loaded with timolol maleate in a variety of ratios. To improve the printing of the contact lenses, the filaments were mechanically and physicochemically characterized. FDM technology could be employed to manufacture 3D-printed lenses with a defined aperture (opening). The lenses had a smooth surface with high printing quality and released timolol maleate steadily over a period of three days. The results of this study can be applied to the future creation of personalized DECL.

Delivering antibiotics

Around 5% of the globe's population suffers from debilitating hearing problems, which affects roughly one-third of those over the age of 65. Hearing aids are routinely used in this demographic, although extended usage can lead to ear infections.

3D printing can also be utilized as a flexible manufacturing method for producing greater patient-specific medical products with antibacterial qualities. A study done in Spain used 3D printing to create hearing aids containing two antibiotics, ciprofloxacin and fluocinolone acetonide.

In the study, hearing aids were made using digital light processing 3D printing with two polymer resins, ENG hard and Flexible.[5] The antibiotics had no effect on the mechanical qualities of the hearing aids. All multidrug-loaded devices exhibited a hydrophilic surface, good blood compatibility, and anti-biofilm action against P. aeruginosa and S. aureus. Hearing aids containing ciprofloxacin and fluocinolone acetonide exhibited sustained drug release for more than two weeks and prevented biofilm development on the device's surface as well as bacteria growth in the surrounding medium.

In another example, researchers proposed the use of biodegradable and biocompatible polymers to create intravaginal devices that could deliver antibiotics over an extended period of time.[6] Bacterial vaginosis is an abnormal condition caused by changes in the microbiota of the vagina. Gardnerella vaginalis is one of the most common bacteria found in cases of BV and is categorized as an anaerobic facultative bacteria. Antibiotics, such as metronidazole (MTZ), are currently the most common treatment for BV, but they require multiple administrations, which can be inconvenient for patients.

The researchers utilized semi-solid extrusion (SSE) 3D printing to manufacture the intravaginal devices. To determine the effect of the polymer composition on drug release, they varied the ratio of high and low molecular weight poly(caprolactone) (PCL). The SSE 3D printer's versatility was leveraged to produce two different shapes (meshes and discs) of the devices, which contained two different layers of polymers. The polymers were composed of PCL and a copolymer of methyl vinyl ether and maleic anhydride that provided mucoadhesive properties. Gardnerella vaginalis growth was inhibited by disc formulations with a zone of inhibitions demonstrating their antibacterial capabilities.

MTZ release was influenced by the design of the devices, with the increased surface area of the meshes giving a quicker release. Since it delivers prolonged release of MTZ and lowers the frequency of administration, this novel technique presents a beneficial alternative to available treatment options while also enhancing patient satisfaction.

A 3D transformation

3D printing has the potential to transform the pharma industry. The technology will help the industry to shift away from conventional methods used for the mass manufacture of drugs and towards the on-demand production of highly flexible, individualized dosage forms.

Recent innovations in pharmaceutical 3D printing

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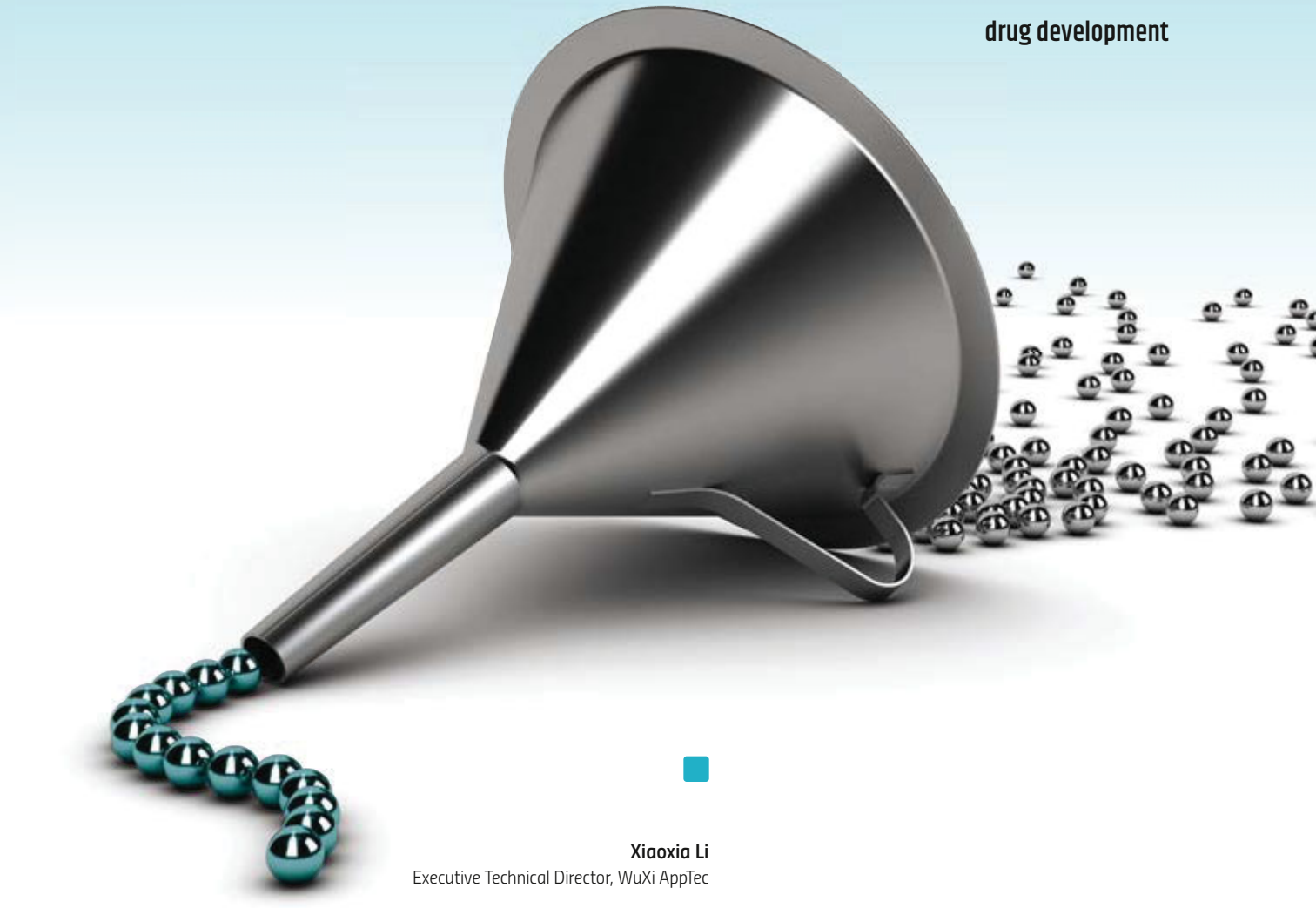

Xiaoxia Li
Executive Technical Director, WuXi AppTec

Streamlining HPAPI development

How to manage highly potent APIs through a preclinical testing process

High-potency active pharmaceutical ingredients (HPAPIs) are a rapidly growing segment of the pharmaceutical industry. In fact, the $7 billion market for HPAPIs in 2022 is expected to reach almost $15 billion by 2030, led primarily by a growing demand for oncology drugs.[1] Higher potency drugs have the potential to achieve similar efficacy at a lower dose than other APIs, which is appealing to drug developers because it minimizes patient exposure to the medication.

HPAPIs make up a significant proportion of new drugs under development. Due to their cytotoxic nature, manufacturers of HPAPIs and the resultant drug products are faced with onerous manufacturing challenges. These drugs require heavy investment to ensure a safe environment for employees. For drug substance manufacturing, the HPAPI may be a small molecule, biologic or a hybrid of the two such as an antibody-drug conjugate (ADC).

Based on therapeutic application, the HPAPI market has been segmented into oncology drugs, anti-diabetic drugs, cardiovascular drugs, CNS drugs, musculoskeletal drugs and other drugs.

The oncology drugs segment has seen a steep rise in the introduction of innovative therapeutic options. ADCs, antibodies and cytotoxic drugs account for the largest share; collectively, they are considered to be the key drivers of the HPAPI market.

With the growing interest in these drugs comes a greater prerogative to properly assess toxicity through preclinical testing.

Defining HPAPIs

Simply put, HPAPIs are pharmaceutical ingredients that have a biological effect at a very low dose. The substance used to develop drugs with HPAPIs does not differ significantly from processes used for less potent pharmaceutical ingredients, but safety concerns arise with manufacturing and handling. Because HPAPIs' strength presents an inherent potential for cytotoxicity, lab personnel and manufacturing facilities need to be protected. In addition to specialized handling procedures, developing HPAPIs may also require designated equipment to contain, store and manufacture the drug product. These specialized facilities require a significant monetary investment above and beyond what would normally be required under good manufacturing practice (GMP) guidelines.

Traditional examples of HPAPIs are cytotoxic compounds and sex hormones such as estrogen. However, any type of compound can be highly potent if it causes a response at a low dose. HPAPIs can fall into one of five categories:

- A pharmacologically active ingredient or intermediate with biological activity at approximately 150 µg/kg of body weight or below in humans (therapeutic daily dose at or below 10 mg)
- An API or intermediate with an Occupational Exposure Limit (OEL) at or below 10 µg/m3 of air as an 8-hour time-weighted average
- Sex hormones and certain steroids (e.g., corticosteroids)
- A pharmacologically active ingredients or intermediate with high selectivity (i.e., ability to bind to specific receptors or inhibit specific enzymes) and/or with the potential to cause cancer, mutations, developmental defects or reproductive toxicity at low doses
- A novel compound of unknown potency and toxicity

These categories span small molecules, large molecules and ADC therapies. The presence of a HPAPIs has an outsized impact on the manufacturing and handling of a drug, but little impact on the safety assessment (including toxicology and drug metabolism and pharmacokinetics studies) that must take place prior to an investigational new drug (IND) submission.

Testing HPAPIs

As a standard practice for safety assessment, animal species selected for toxicity assessment require scientifically sound justification. This is also applicable to designing the toxicology program for HPAPIs.

Toxicology testing is designed based on the property of the testing material (i.e., small molecule, large molecule or ADC) but not the potency of the active ingredient. To test potency, the following methods are most common:

- High performance liquid chromatography (HPLC) is used to separate a mixture of compounds to identify, quantify or purify its individual components. HPLC is the preferred method to determine potency in HPAPIs due to its specificity and efficiency. This method can be used to determine drug stability as well, but not predictably. Only a validated stability-indicating method (SIM) can reliably measure an API's chemical, physical and microbiological properties over time.
- Titration is a quantitative method that measures an API's chemical reaction with a known analyte. Titration uses bacteria to assess the antimicrobial activity of an API in relation to a microorganism. These microbial assays measure zones of inhibition, or areas around the spot of the antibiotic in which bacterial colonies do not grow. These zones measure the bacteria's susceptibility to the antibiotic. A larger zone of inhibition usually means a more potent antimicrobial.
- Ultraviolet-visible spectrophotometry can be used without chromatography to determine the potency of a single analyte in a solution. By measuring the amount of light absorbed by a chemical substance, UV spectrophotometry can determine concentrations, identify unknown compounds, and provide information about the physical and electronic structures of organic and inorganic compounds. This method is susceptible to erroneous results if compounds interfere with absorption, thus increasing toxicological concern.

The drug safety assessment process during preclinical testing can be costly and time-consuming, but ultimately impacts patient safety.

Animal species are then selected based on metabolism profile for a small molecule drug. As such, a series of in vitro and in vivo assays need to be conducted in order to select appropriate animal species that will be employed in the subsequent toxicology studies. In most cases, one rodent and one non-rodent animal species are selected for safety evaluation. On the other hand, only pharmacologically relevant animal species are selected for a biologic toxicity assessment based on binding profile. For example, a mini pig's skin and heart are similar to a human's skin and heart, making mini pigs the best choice for testing internally applied compounds. Conversely, a non-human primate's immune system is closer to a human's than a mini pig or a canine; thus, they are often the most appropriate species for toxicology testing.

There is no specific regulatory requirement pertaining HPAPIs when designing a toxicology program, but toxicological data plays an important role in establishment of OELs, which subsequently impacts how those active pharmaceutical ingredients are handled further downstream in the manufacturing process.

Balancing benefit and risk

Preclinical testing for drug development, whether synthetic or biologic, is a multistep process requiring scientific expertise and technical experience as well as

regulatory guidance. These steps involve multiple studies that can add significantly to drug development timelines, so thoughtful program design is critical to a streamlined submission process.

Specifically, an increased toxicity profile is likely to be associated with an HPAPI due to its high potency. Consequently, toxicity assessment for an HPAPI becomes more challenging than for a less potent API. For example, with a small molecule HPAPI, the efficacy and metabolism profiles are usually established prior to conducting toxicology studies that include (but are not limited to) genotoxicity, and single and repeat dose toxicities in both rodent and non-rodent species.

The drug safety assessment process during preclinical testing can be costly and time-consuming, but ultimately impacts patient safety. Regulators will appreciate preclinical testing outcomes with strong methodology come IND submission.

A final word

There is no denying that HPAPIs pose significant therapeutic promise for cancer and other diseases. But these pharmaceutical ingredients can also pose significant safety risks for patients and those involved in the manufacturing and handling of the drug if they are not properly controlled.

In addition to potency and efficacy, HPAPIs present stability challenges that must be addressed through specific assays designed to alleviate toxicological concern.

While a pharmaceutical ingredient's status as an HPAPI does not directly impact its preclinical testing path, the results of toxicity assessment can relay important information about OELs and other manufacturing and handling limitations ahead of clinical trials.

Preclinical testing for HPAPIs is a lengthy and intricate process, but a quality laboratory testing partner can help mitigate that complexity, potentially streamlining the IND/NDA application process.

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1 | *High Potency API Contract Manufacturing Market Size, Share & Trends Analysis Report by Product Type. Grand View Research. (2022).*

Francesca McBride
Director, Regulatory Compliance, Jacobs

Powering progress in cell therapy

Getting transformative treatments to market will require rethinking processes and facilities

Personalized medicine plays a central role in delivering better patient outcomes and provides the long-term promise to treat and potentially cure a broad range of conditions. In recent years, there has been an increase in research and development of these advanced therapy medicinal products, a broad category that includes cell and gene therapies and RNA therapeutics.

However, the processing equipment used in cell therapy (CT) manufacturing originates in research labs where it was intended for single use or individual process steps. It was not designed with commercial manufacturing in mind.

Pharma manufacturers and solutions providers need to work in partnership to respond to manufacturing challenges with fresh thinking that puts a focus on automated and integrated solutions, supported by a flexible approach to facility design.

Impact on facility design

The main approaches adopted for CT manufacturing are 'all in one,' which uses a single and almost fully-automated piece of equipment for the whole process, and modular, where an individual piece of equipment is used for each step. Both approaches have advantages and drawbacks: The former can lack flexibility, while the latter equates to manual, open processing, which increases contamination risk.

At the same time, CT manufacturers face data challenges, including integration, quality, management, complexity and interoperability; for example when connecting different machines and equipment during the processing phase. Additionally, there is a need for equipment to connect to wider manufacturing systems within the supply chain.

CT manufacturing requires sterile manufacturing as the processes do not include terminal sterilization via sterile filtration and not all process operations are closed. Manufacturing also requires high containment levels. The product maintains the same biosafety classification throughout, which is important due to the broad utilization of viral vectors in processing. When new process steps are added, it is necessary to assess biosafety levels and understand the overall risk to the facility.

These challenges impact facility design and cost — at the same time, manufacturers must ensure facilities meet regulatory requirements.

Reimagining manufacturing

New developments in equipment and technology, coupled with fresh and innovative thinking, are powering progress in CT manufacturing. Strategies that rethink the overall process and reimagine how different manufacturing steps work are at the heart of addressing challenges.

This thinking involves merging different machines, reducing the need for the human-machine interface, reducing the number of batches run — especially in R&D — and intensifying the process operations space.

Best practice in the automation of processing equipment focuses on: 1) combining different steps in a smaller number of machines to reduce the number of open steps and, ultimately, shortening the time needed to move product from A to B; 2) deploying flexible processing equipment to allow manufacturers to change the process without the need to alter the setup.

Emerging digital solutions will also play a role and will support the implementation of automation strategies around product analysis, decontamination, biosafety and processing. To improve and streamline production, an increasing number of sensors are being integrated in manufacturing equipment. This approach allows data to be extracted from a myriad of sources across the manufacturing landscape.

A flexible approach to planning facilities is vital for categorizing viral vectors at the appropriate biosafety and containment levels. Flexibility will also ensure that biosafety levels and the overall risk to the facility are assessed if new process steps are added. From a regulatory perspective, FDA and the EU's Annex 1 guidelines deem flexibility acceptable.

Requirements are subject to change, as developers often work on different therapy modalities with different approaches and processes as well as different needs for scale-up/scale-out to meet demand.

The growing success and effort in the development of CT provides a significant opportunity to achieve improved patient outcomes and the long-term potential to eliminate serious diseases.

Strategic review and input: Paolo Siciliano, Ph.D., Head of Cell & Gene Therapy, PA Consulting

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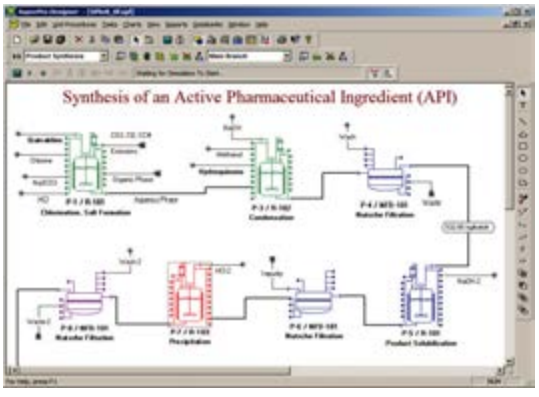

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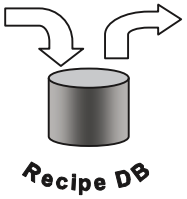

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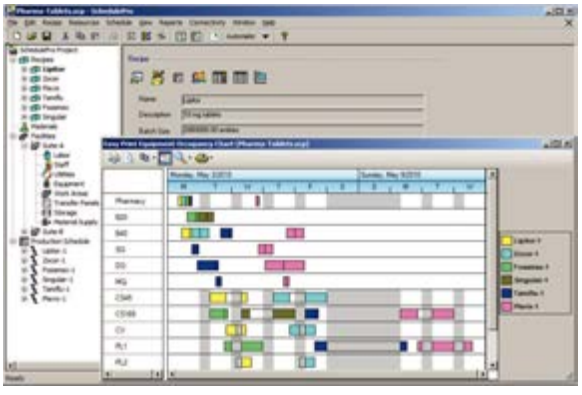

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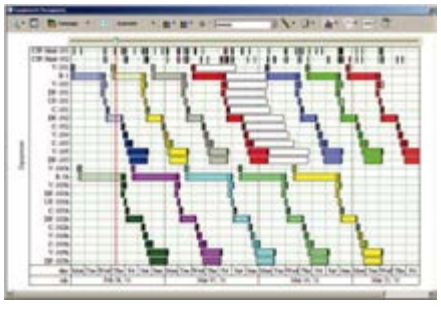

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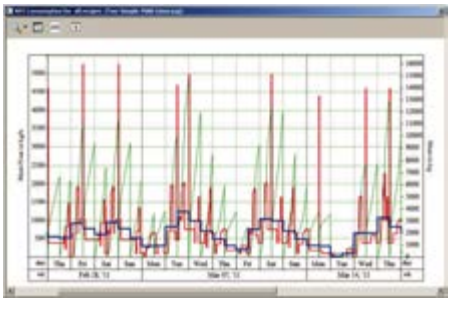
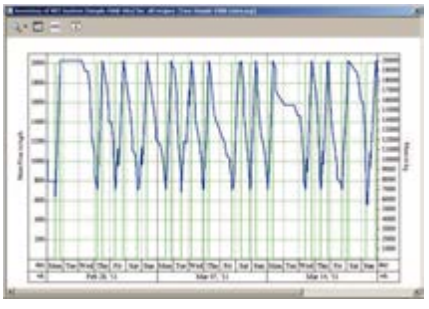


Tracking demand for resources (e.g., labor, materials, utilities, etc.)



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

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Beyond empty and full

Understanding heterogeneity in rAAV products and impurities

It's an exciting time in gene therapy, with the recent approvals of lifesaving products where few (or no) treatments used to exist. Like the rapid biologics boom in the 1980s, significant improvements are being made in manufacturing and testing.

Currently, recombinant adeno-associated virus (rAAV) is the most common viral vector used for the in vivo administration of gene therapies. Despite the demonstrated success of rAAV products, several instances of treatment-emergent serious adverse events (TESAEs) — some even leading to patient deaths — have occurred following intravenous administration at high doses. The field is in critical need of a more detailed product understanding in order to increase product safety without sacrificing efficacy.

Standardizing characteristics

rAAV are complex biologics composed of ~60 assembled viral proteins which form the protein capsid 'shell' along with an internal DNA sequence carrying the necessary elements for therapeutic effect. An innate level of heterogeneity (diversity, variation) in product and product impurities exists in rAAV within both the protein and the DNA sequence. Heterogeneity can impact safety, efficacy and product quality. Broadly, heterogeneity in rAAV can be classified into the following categories:

- Heterogeneity in encapsidated rAAV DNA sequence lengths
- Heterogeneity in rAAV DNA sequence identity and composition
- Heterogeneity in rAAV capsid protein integrity, stoichiometry and post-translational modifications

Understanding these product attributes and their role in product safety, efficacy and quality is critical, particularly because many rAAV products target rare indications with aggressive disease phenotypes. After a number of TESAEs occurred following treatment with high dose, systemic rAAV products, an FDA advisory committee met in September 2021 to discuss toxicity risks. While a singular root cause of the TESAEs was not identified, a total capsid dose correlation emerged.

The total capsid dose is typically calculated from both the overall dose (the number of 'full' capsids, measured in vg/kg) and the percentage of empty capsids (viral particles that don't contain any DNA). While empty capsids are considered an impurity in rAAV products and likely play a role in immunogenicity, there are additional impurities and variants that can contribute to the quality profile, such as capsids that do not contain the correct length of DNA (aka 'partial' or 'overpackaged' capsids) or those that don't contain the correct DNA sequence. Some of these are not routinely characterized in rAAV products and require greater analytical standardization across products.

Improving measurement

Historical rAAV analytical methods have not been sensitive enough to quantify both a product's heterogeneity and its product-related impurities. Methodologies for quantifying this heterogeneity are advancing rapidly, enabling a more comprehensive understanding of characteristics than has been historically possible. These advances provide the possibility of characterizing rAAV to a higher standard but have yet to be widely adopted. As the rAAV field advances and matures, sponsors may see increased standards aligning with harmonized guidelines, such as those described in ICH Q6B.

A subset of product heterogeneity currently receiving increased focus is capsids containing a shorter-than-intended DNA sequence. Termed 'partial capsids,' the identity of the included partial sequence can determine whether it contributes to the therapeutic effect. Advancements in Next-Generation Sequencing (NGS) methods paint a picture of sequence identity, size distributions and relative abundance within individual capsids. Additionally, NGS provides a window into product-related heterogeneity that can impact efficacy, efficiency and safety of rAAV products. While NGS and other analytical methods have provided drastic advancements in rAAV heterogeneity characterization, there are still significant limitations for implementation to be addressed.

While rAAV characterization has improved substantially, there is still a long way to go. In a recent white paper, Dark Horse Consulting sought to classify heterogeneity and impurities in rAAV products, discuss emerging technologies for characterization, and introduce how these attributes can improve product understanding and further define manufacturing strategy. With these advancements, there is an opportunity to gain greater understanding of rAAV product heterogeneity and related impurities, which will allow for better product quality understanding across the gene therapy industry — paving the way for the development of safer and more efficacious rAAV products.

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