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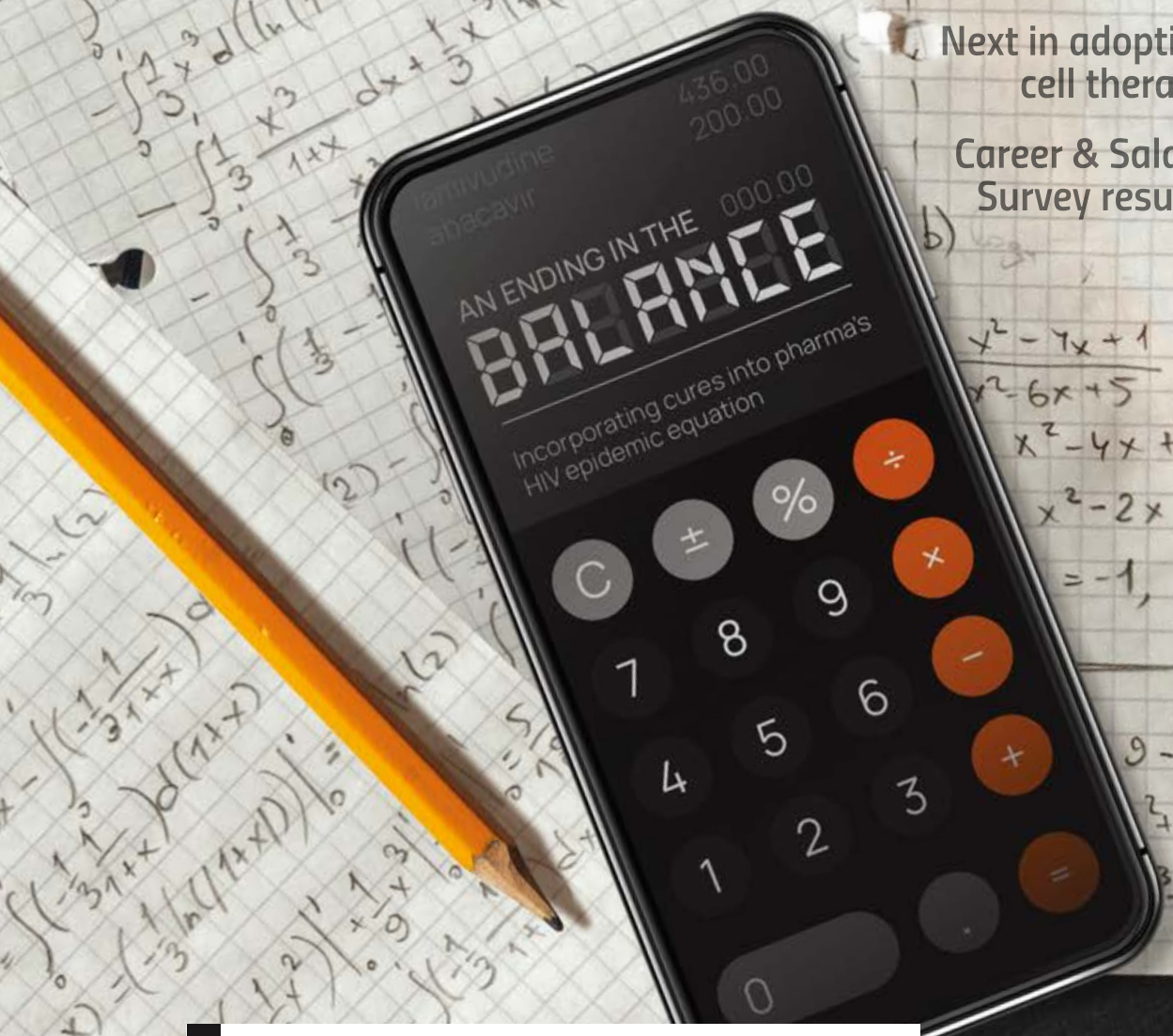


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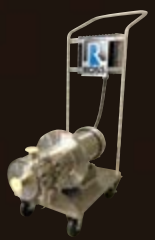


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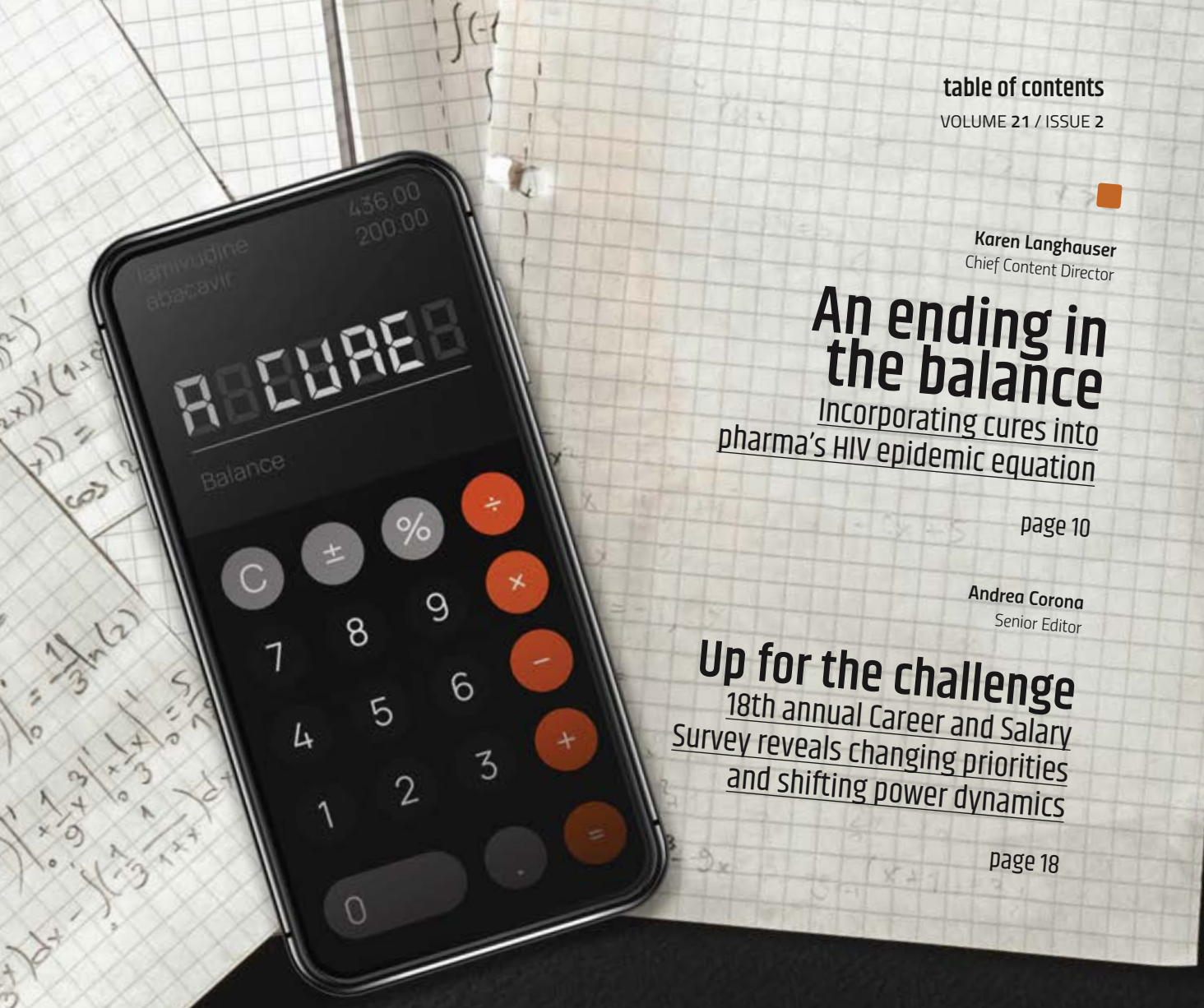


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Chief Content Director

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

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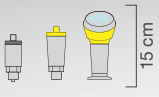


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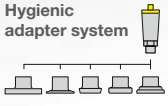

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**Karen Langhauser**
Chief Content Director

# Remembering the remainders

Every person counts when calculating the end of the HIV epidemic

The most amazing thing happened while I was writing this month's cover story — my numbers were off. In the time it took me to complete an article about ending the HIV epidemic, the total number of people cured of HIV changed from two to three.

This number may seem insignificant when considered alongside all the other numbers involved in the HIV epidemic: 37.7 million people are living with HIV. 1.5 million people were newly infected with HIV in 2020. 36.3 million people have died from AIDS-related illnesses since the start of the epidemic.

And yet, to the American woman who has shown no evidence of an 'HIV rebound' in the 14 months since stopping her antiretroviral treatment regimen, subtracting one person from the total matters.

Ending the HIV epidemic has very much been about the numbers. Mathematical modeling has long been used as a tool to analyze and understand HIV infection and transmission dynamics and to propose mitigation measures to control the spread.

Recently, a Johns Hopkins Medicine research team developed a mathematical model to help end the HIV epidemic in the U.S. The algorithm splits each city's population into categories of race, age, sex and HIV risk factors — and estimates the number of HIV infections associated with each. From there, the model can predict what would likely happen if cities adopted particular interventions.

The model is being utilized in the Ending the HIV Epidemic in the U.S. initiative, which, like many epidemic-ending plans, has a goal date of 2030. Global and federal health agencies around the world are pushing to meet individually defined targets over the next eight years. Researchers and industry have also joined the race — but everyone has a slightly different version of what 'ending the epidemic' looks like and unique plans to get there.

HIV has always been a complex problem to solve, both from a pharmacologic and socioeconomic perspective. Approaches to treatment and prevention have evolved greatly over the last 40 years, putting the end of the HIV epidemic seemingly within reach.

But what mathematical models and federal initiatives rarely factor into the math is a cure — and for the 37.7 million people with HIV who face a lifetime of antiretroviral therapy, that matters.

Fortunately, the cure research space is buzzing with enthusiasm. On the pharma side, the efforts are multi-pronged and collaborative, with most companies acknowledging that there will be no silver bullet, single cure to the notoriously stealth virus.

Whether it's engineering arenaviruses to deliver virus-specific genes directly into patients to evoke a T-cell response; utilizing broadly neutralizing antibodies and engineered HIV inhibitors to identify and eliminate the dormant HIV that may be hiding in human cells; or even using CRISPR/Cas9 gene editing to remove the HIV genome integrated into infected cells — the pharma cures space is full of promising science.

Treatment and prevention may be the lead tools for ending the HIV epidemic, but cures give people hope. And to those for whom the HIV epidemic is personal, even a nascent and modest cures pipeline makes a difference.

As we move towards a future that may no longer include an HIV epidemic, we remember a past where AIDS activists took to the streets of New York demanding to be heard. Included in this final equation should be the most historically influential factor — the voice of people who refuse to be counted out.

**Andrea Corona**
Senior Editor

# What pharma's top work spots are doing right

## A look at how the best companies to work for are keeping employees happy

Back in January, Glassdoor rolled out its ranking of the 100 Best Places to Work in 2022, and four pharma companies made the list.

This is not necessarily surprising, as Pharma Manufacturing's annual Career and Salary Survey (page 18) has shown that pharma professionals are mostly content with their careers. This year, more than 89% of respondents reported their satisfaction levels within the range of 'very high' to 'okay.'

Our survey also showed that pharma is not immune to the issues plaguing the rest of the world. As we live through what experts are calling the 'great resignation,' employee retention and developing company culture have never been more important.

Here are the four pharma companies doing the best at keeping people happy:

### 1. Merck (#46)

Merck is the highest-ranking among the pharma companies featured on the list, coming a long way from its spot last year, at #63. Employees highlighted the company's excellent leadership, pleasant work environment and the fact that Merck provides great benefits.

And it's not just the employees recognizing Merck's leadership. The company's former CEO, Kenneth Frazier, was included in Glassdoor's Top CEOs of 2021 list.

### 2. Roche (#74)

Considering the company is based in Switzerland — the third happiest country in the world, according to the 2021 World Happiness Report — Roche was set up for success. Employees gushed about benefits, purpose and overall company culture.

Purpose and the ability to do meaningful work came up on Pharma Manufacturing's survey this year as a top priority for pharma professionals. One respondent said that what satisfies them most in their current role is "making products that help society."

It seems that Roche prioritizes making their mission and vision known, and it shows.

### 3. Johnson & Johnson (#75)

Right behind Roche, we find pharma giant Johnson & Johnson. 2021 was a wild ride for the company, as they received numerous workplace awards and navigated the rough waters of COVID-19 vaccines.

While still commendable that the company made the list, J&J stumbled from its 24th spot last year.

### 4. Pfizer (#94)

Although the company just snuck into the top 100 in the 94th slot, Pfizer employees were pleased with the work environment and company benefits, and mentioned that Pfizer is great for networking building.

Pfizer employees boasted that the company's culture promotes professional growth and development. The desire for this was a common motif in this year's Career and Salary Survey. Many respondents mentioned the lack of opportunities for growth within their company as a source of dissatisfaction in their current role. Frustration due to "overcrowded work environments," and "no room for upward mobility," were among a few of the issues shared.

Considering that global pharmaceutical revenues totaled $1.27 trillion in 2020, there should be no shortage of resources to expend in the industry.

But today's employees are driven by more than just money, and companies must make the changes necessary to meet the demand of this wave of professionals who are not afraid to speak their minds and ask for what they want.

The modern workforce has requests, and smart pharmaceutical companies are listening.

INFOGRAPHIC

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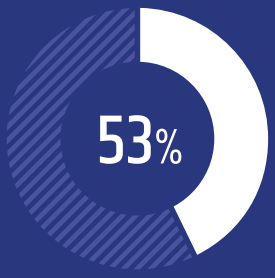
# Hidden costs of manually managing pharma waters

While the cost of real-time monitoring technology is a major barrier to adoption in the pharma industry, using this technology ultimately leads to less costly problems — and less problems overall.




of pharma plants still rely solely on grab samples for microbial testing of pharma waters

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**Karen Langhauser**
Chief Content Director

It started with an impassioned appeal for survival. Staring down a terrifying diagnosis with an average life expectancy of one year, patients and their advocates were screaming for a cure.

During the gap between the first published cases of severe pneumonia infecting otherwise healthy gay men in the summer of 1981 and the first Food and Drug Administration-approved medication in March 1987, over 40,000 cases of AIDS were reported to the World Health Organization. The agency estimated that it was likely that 5 to 10 million people were living with HIV infections worldwide.

Pharma companies began scouring their shelves, looking for compounds with the potential to combat AIDS, while cases and deaths continued to catastrophically mount. Burroughs Wellcome sent its nucleoside reverse transcriptase inhibitor, azidothymidine (AZT) — which failed years earlier against cancer but had showed promise against mouse and cat retroviruses — to the National Cancer Institute for further testing. Just six months after favorable lab reports from NCI, in July 1985 AZT was injected into a human for the first time — 20 months later, it had the first FDA approval.

The historically controversial approval — which at first was limited to only those who were severely ill with AIDS — brought about broader realizations about what science was up against in the AIDS fight. AZT's toxicity led to brutal side effects and over time, patients began developing viral resistance to the drug. Although crucial to paving the way for future treatment regimes, it quickly became clear that AZT alone provided only modest benefit to those dying from AIDS — and certainly was not the silver bullet cure for which patients had been hoping.

Focus shifted towards finding new and safer treatments — and combinations of treatments — that could more effectively treat both HIV and AIDS. While the quest for a cure was never abandoned, many in the scientific community argued that given the constantly mutating virus and its stealth ability to hide in cell reservoirs, a cure might never be possible.

Now, over 40 years later, the FDA has approved over 60 drugs in the buzzing HIV treatment and prevention space.[1] With combination drug treatments started early, people living with HIV can not only survive but can potentially remain undetectable and unable to transmit HIV — living near-normal lifespans. Despite three isolated cases of individuals cured of HIV while undergoing invasive treatments for cancer, a scalable cure has yet to be found.

But the voices of those living with HIV are still ever-present and many engaged in the fight have united in an ambitious goal: ending the HIV/AIDS epidemic. The target year is 2030. In the U.S., there are two national plans in place to help stick to that timeline. Globally, the Joint United Nations Program on HIV/AIDS (UNAIDS) has set the same 2030 deadline.

There are many parameters being used to define the epidemic's 'end' and just as many plans to get there. But few, if any, federal or global initiatives expressly specify the need for a cure.

Pharma, however, has its own plan. Within the industry, optimism is high regarding the feasibility of ending the HIV epidemic. This race to the end has become a delicate — and at times, conflicting — balancing act between the hunt for continued innovation in a crowded treatment space and the ongoing, collaborative search for a cure. Ultimately, pharma's ability to weigh these pursuits could pay off exponentially for both the industry and people living with HIV.

## A formula for the end

The succinctness of the call to 'end HIV by 2030!' makes it highly effective as a rallying cry, but confusing as a quantitative goal. Ultimately, the objective is the end of HIV/AIDS as an epidemiologically-defined term, using certain criteria to measure progress.

In the U.S., the HIV National Strategic Plan uses viral suppression as the main indicator of success. Specifically, the U.S. goal is for 86% of people living with HIV to be virally suppressed on antiretroviral treatment by 2030.[2]

If no other factors were considered, epidemiologically, HIV could end without a cure. Given how lucrative the HIV treatment space has been for pharma companies (the industry's top-selling treatment, Gilead's single-tablet blockbuster, Biktarvy, is predicted to achieve sales of around $11 billion by 2025) it may seem contradictory that a company would pursue something — in this case, a cure — that could, in theory, make treatments obsolete.

**79.3 million people have become infected with HIV since the start of the epidemic.**

But taking into consideration the vast amount of human lives affected, the myriad variables that come into play in the complicated HIV treatment landscape, and the commitment to end the epidemic by 2030, many pharma companies active in the HIV market have made the hunt for a cure a dedicated part of their epidemic-ending plans.

Pharma's approach to ending the epidemic has evolved over years of observing the patient experience, and that evolution has brought the industry closer to a cure.

Currently, an estimated 38 million people are living with HIV, facing a lifetime of antiretroviral therapy.

"The need for lifelong treatment of HIV with antiretroviral therapy poses multiple challenges for people living with HIV (PLWH)," says Brian Plummer, a spokesperson for Gilead Sciences.

PLWH often struggle with treatment fatigue or pill burden. Side effects from lifelong antiretroviral therapy (ART) regimens can include weight gain, muscle pain, nausea and insomnia. Living with HIV also means confronting numerous social and psychological challenges.

The confluence of these factors can lead to poor drug adherence, which can result in drug resistance and suboptimal viral suppression rates — a direct contradiction to epidemic-ending goals. On the flip side, heavily treatment-experienced patients may also struggle to maintain viral suppression with currently available medication due to drug resistance.

Additionally, while the scientific advances made in the HIV space have fortunately led to substantial improvements in the life expectancy of people living with HIV, this too comes with challenges and a new set of considerations.

"The corollary of a longer lifespan is that PLWH are now faced with an increased risk of developing comorbidities and chronic diseases associated with aging, in addition to chronic HIV. Chronic comorbidities may also contribute to a greater pill burden and additional complications, which may negatively

## Ending the epidemic:

### Progress towards 95-95-95 by 2030

84%

In 2020, 84% of people living with HIV were diagnosed

87%

Among those diagnosed, 87% were accessing treatment.

90%

Among people accessing treatment, 90% were virally suppressed.

SOURCE: UNAIDS

impact adherence to HIV therapy," says Plummer. "Achieving a cure would have a dramatic impact on the challenges associated with lifelong treatment and the social stigma associated with HIV and is key to accomplishing the shared goal of ending the HIV epidemic."

But lacking immediate prospects for a cure, the pharma industry has looked to address unmet patient needs with innovative, more convenient treatment solutions.

According to Kimberly Smith, M.D., MPH, head of R&D for ViiV Healthcare, "For the past decade, it felt like we had reached a plateau in how we treated HIV with once-daily oral HIV medicine. Once-daily oral medicine has been and remains the bedrock of our approach to treatment, but for many individuals, it can be challenging and to continue our progress towards ending the epidemic, we must look for innovative options beyond daily medicine."

Davinderpreet Singh Mangat, Informa Pharma Intelligence senior analyst with a focus on infectious disease research says a change in treatment paradigms is already underway.

"There will likely be a continued shift towards developing long-acting regimens and that will become the new normal in 5-10 years' time," says Mangat.

ViiV's Cabenuva, approved by the U.S. FDA in January 2021, was the first-ever, long-acting HIV treatment. It is administered via injection every two months instead of daily, significantly reducing dosing from 365 to as few as six times a year. ViiV — which was born out of a partnership between GlaxoSmithKline and Pfizer in 2009, with Shionogi joining in 2012 — anticipates that between 10% and 15% of eligible patients will switch to Cabenuva from daily oral therapy.

Gilead's most recent prospect, lenacapavir, is an investigational, long-acting HIV capsid inhibitor that could also facilitate treatment adherence by increasing dosing convenience. Lenacapavir is currently being investigated for use alone for HIV prevention or in combination with other antiretroviral agents for HIV treatment; as oral or injectable delivery, with potential multiple dosing frequencies, some as little as twice per year. (While Gilead recently hit a regulatory snag when the FDA declined to approve the treatment due to lenacapavir's compatibility with the vials it's stored in, the drugmaker is working with the agency to rectify its vial problem.)

"The next major breakthroughs will be about providing options that allow people to go even longer between their HIV treatments, like medicines administered twice or even once a year," says Smith.

These treatment innovations have also helped nudge pharma closer to a cure. Functional cures — a scenario where treatments trigger long periods of viral remission in the absence of ART — could advance progress a step further than current long-acting treatments, potentially allowing people to go years between taking medicine.

### Keeping tabs on the cure market

Despite the long-standing buzz surrounding the hunt for a cure, quantifying that interest — especially from the pharma industry — is challenging.

Leaders in the pharma space have backed their commitments to a cure with large amounts of funding initiatives and philanthropic leadership.

For example, Gilead's HIV cure grants program has awarded more than $29 million in grants to academic institutions, non-profit organizations and community groups engaged in HIV cure activities since initially announced in February 2016.

ViiV Healthcare and GlaxoSmithKline have collectively invested $40 million into a collaboration with the University of North Carolina at Chapel Hill, out of

# cure pipeline snapshot

**AbbVie** | **phase 1:** ABBV-1882 is a combination of AbbVie's budigalimab, an anti-PD1 mAb and ABBV-382, an anti-a4b7 mAb, being investigated as a functional cure for HIV.

**American Gene Technologies** | **phase 1:** AGT103-T is a single dose autologous cell therapy currently being tested as a one-and-done HIV cure in the RePAIR trial.

**MacroGenics, NIAID** | **phase 1:** MacroGenics, under a contract awarded by National Institute of Allergy and Infectious Diseases, completed a phase 1 study evaluating MGD014, a bispecific dual-affinity re-targeting (DART) molecule, in persons with HIV maintained on ART. A phase 1 study of DART molecule MGD020 alone and combined with MGD014 will initiate in 2022, with the goal of both molecules becoming part of a strategy to reduce/eliminate latent HIV reservoirs.

**Excision BioTherapeutics** | **phase 1/2:** EBT-101 is a CRISPR-based therapeutic that utilizes an adeno-associated virus to deliver a one-time intravenous infusion intended to functionally cure HIV infections.

**Gritstone Bio, Gilead Sciences** | **phase 1:** Testing an HIV-specific therapeutic vaccine that uses Gritstone's proprietary prime-boost vaccine platform, comprised of self-amplifying mRNA (SAM) and adenoviral vectors, with antigens developed by Gilead towards the end goal of a curative treatment for HIV.

**Gilead Sciences** | **phase 1b:** Elipovimab is a first-in-class effector-enhanced broadly neutralizing HIV-1 antibody (bNAb) being tested towards the goal of reducing or eliminating the HIV reservoir in patients.

**Rockefeller University, Gilead Sciences** | **phase 2:** Two investigational broadly neutralizing antibodies (bNAbs) – GS-5423 and GS-2872 – developed by Rockefeller University and licensed by Gilead are being evaluated for use in HIV cure strategies.

**Gilead Sciences** | **phase 2:** Lefitolimod, a toll-like receptor 9 (TLR-9) agonist being investigated as part of a functional cure for HIV by Aarhus University Hospital in collaboration with Gilead

**AELIX Therapeutics, Gilead Sciences** | **phase 2:** The AELIX-003 trial is evaluating a regimen of Aelix's HTI T-cell immunogen vaccine and Gilead's vesatolimod, an oral toll-like receptor 7, towards the end goal of achieving a functional cure of HIV infection.

**GeoVax** | **phase 1:** In collaboration with researchers at the University of California, San Francisco, the GOVX-B01vaccine is being tested as part of a combinational therapy towards the end goal of achieving a functional cure of HIV infection.

**ViiV Healthcare** | **phase 2:** N6LS, ViiV's broadly neutralizing antibody (bNAb), is being tested in the HIV cure space.

which came Qura Therapeutics and a dedicated HIV Cure Center.

The AIDS Vaccine Advocacy Coalition (AVAC) and the International AIDS Society's most recent Global Investment in HIV Cure Research and Development report indicated that global investment in cure research has been on the rise, hitting $328.2 million in 2019. All signs point to that number growing, especially given the National Institutes of Health's recent decision to award approximately $53 million in annual funding over the next five years to 10 research organizations in a continued effort to find a cure for HIV.[3]

These numbers, however, primarily consist of funding tallies from the public sector and philanthropies — AVAC acknowledges that industry funding is missing from those totals.

In terms of cures in the pharma pipeline, there are currently less than a dozen specified 'cures' in early-stage trials, five of which fall within market leader Gilead's pipeline.[4,5]

Mangat notes that because there are no approved cures for HIV and that "candidates tend to go in and out of the pipeline," the cure market generally gets rolled into the treatment market for assessment purposes.

In reality, the line between treatment and cures has become increasingly blurred with the proliferation of functional cures, which essentially trigger a state of 'HIV remission.'

"Because what we are mainly talking about at the moment are functional cures, some of the HIV treatment pipeline consists of potential therapies that could offer a cure as well," says Mangat.

Klaus Orlinger, Hookipa Pharma's executive vice president of research, says that, in his experience, the designation between a potential cure and treatment can't be made until clinical trials begin, although there are generally preclinical indicators.

"Together with our partners, we did run preclinical studies that make us believe that our vector can make a significant difference in this patient population, but you cannot mimic the situation of HIV positive patients that have previously been on ART in a preclinical model. That has to be addressed in a phase one clinical trial," says Orlinger.

Hookipa, together with partner Gilead, plans to use its proprietary technology to design arenavirus vector-based vaccines, as part of a functional cure for HIV.

If Hookipa's trial begins as anticipated in 2023, the company will join a small number of pharma companies with potential cures in the clinical pipeline.

Richard Jefferys, Basic Science, Vaccines and Cure Project director at Treatment Action Group (TAG), a community-based research and policy think tank, says the last decade has brought a greater rise to the prominence of cure research. Part of Jefferys' role at TAG is to update the organization's highly-cited listing of HIV cure-related clinical trials and studies.

TAG's 2021 pipeline report, which catalogs clinical trials and observational studies related to the research effort to cure HIV, listed just over 130 active studies, 19 of which were recently launched. However, the bulk of these trials is sponsored by academia or the public sector, not the pharma industry.[4]

**36.3 million people have died from AIDS-related illnesses since the start of the epidemic.**

However, momentum in the pharma industry is picking up, with several more companies like Hookipa aiming to launch cure-related trials by 2023. Among them, major players Gilead and GSK/ViiV Healthcare. ViiV plans to take its host targeted IAP inhibitor into the clinic this year on the path to demonstrating that the molecule has utility as part of a cure regimen.

Merck, partnered with Boston-based startup Dewpoint Therapeutics, plans to leverage Dewpoint's expertise in molecular condensates to develop an HIV drug candidate with a unique mechanism with the potential to cure HIV.

Los Angeles-based gene-modified cell therapy developer Enochian BioSciences says it also anticipates launching a trial of its potentially curative cell therapy treatment that combines analogous Natural Killer and Gamma Delta T-cells.

If any of these cures were to advance out of the clinic, Mangat says drugmakers will face a new set of market considerations. The durability of the cure will play a big role in the pricing structure, with one-off cures being priced the highest and functional cures priced according to how long they enable life without ART.

"There will be additional considerations in terms of the regulatory process and uptake. It will be quite different from ART, likely more towards what you'd expect for conventional gene and cell therapies," says Mangat.

And, of course, if any company could find the holy grail of HIV treatment, the financial rewards would be considerable.

"Although it can look as if it counteracts the industry's first aim of providing treatment to patients, if one of these companies did manage to find a cure for HIV, it would be very, very lucrative for them," says Mangat.

## Two goals, one stone

While leaders in the HIV treatment space express confidence about ending the epidemic by 2030, they also acknowledge that it's a process — and one that lacks a silver bullet solution. Fortunately, this process is already well underway.

"The reality is that we have the tools to start moving toward the end of the HIV epidemic now," says Smith.

The process is driven by a continued search for innovation, and that innovation has been found by looking to areas of unmet need among the patient population. Key to understanding these needs, and ultimately, solving the puzzle of both ending the epidemic and finding a cure, has been widescale collaboration.

"As we continue innovation to discover a cure for HIV and help bring an end to the HIV epidemic, our partnerships and collaborations are more important than ever," says Plummer. "A multi-pronged approach will likely be needed to achieve the goal of curing HIV. We are working closely with industry, academic and community partners on preclinical and clinical studies and sharing insights from our cure research program that can benefit the entire scientific community."

This sentiment is shared by ViiV as well.

"We realized a long time ago that we could go much further in our efforts if we worked to bring together the best and the brightest in industry and academia to focus on exploring every avenue, mechanism and compound towards our end goal of an HIV cure," says Heather Madsen, Ph.D., head of Bioinformatics and HIV Cure at ViiV Healthcare.

ViiV boasts more than 50 active collaborations worldwide with pharma and biotech companies, government agencies, academic institutions and non-profits. It's industry-academic partnership at

ViiV Healthcare and UNC scientists are part of a joint team based in labs on the UNC Chapel Hill campus, unifying the strengths of a world-renowned public research institution and a pioneering private industry leader.

the UNC HIV Cure Center is the only one of its kind dedicated to finding a cure for HIV.

"[The partnership] combines the best of cutting-edge basic research with the drug discovery and development expertise of pharma and importantly, allows a focused and dedicated effort to accelerate towards a cure," says Madsen.

## Leaving no one behind

Perhaps in no other treatment area are socioeconomic disparities more pronounced than the HIV landscape. These disparities not only affect the goal of ending the HIV epidemic, but are also a driving force behind the search for a cure.

In the fight against HIV, many lower-income countries rely on support from humanitarian aid programs, such as those set up by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and UNAIDS. But questions about the long-term sustainability of such programs create ongoing uncertainty for people living with HIV in lower-income countries.

"There's people right now around the world that worry about what would happen if PEPFAR ended. If a new American president decided that they didn't want to keep supporting that program, suddenly millions of people around the world could have their treatment supply cut off. Part of the impetus for wanting to get to a cure is to eliminate those uncertainties hanging over patients," says Jefferys.

Even in high-income countries, the financial burden of HIV treatment is significant. In the U.S., government spending on the domestic response to HIV has risen to more than $28 billion per year. A cure represents the future possibility of freeing up that spending for other diseases.

From the beginning of the HIV epidemic when activists took to the streets in New York City and stormed the FDA headquarters in Rockville, Maryland to protest, the voice of people living with HIV has been instrumental in inciting progress. Pharma companies in the HIV space have learned to listen to these voices, fine-tune their approaches and engage with the HIV community.

"Our mission is to leave no one living with HIV behind, and as a former physician on the frontlines of the epidemic for over 20 years, I am committed to this, because it ensures that our efforts stay directly grounded in the community of people living with and impacted by HIV," says Smith.

Ultimately, regardless of the mathematical calculation used to reach the end of the epidemic, all people living with HIV are part of the equation.

"When someone living with HIV reads about ending the epidemic, it doesn't really answer the question of when it's going to end for them. That's why it's so important to acknowledge that ending the epidemic will require a cure," says Jefferys.

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**Andrea Corona**
Senior Editor

# Up for the challenge

## 18th annual Career and Salary Survey reveals changing priorities and shifting power dynamics


As a kid, I remember seeing suggestion boxes in places like restaurants and thinking about how much fun it would be to sit down and read through what people said when given the chance to share their anonymous thoughts.

Now, in the age of Yelp, Google reviews, Glassdoor, and the many other business-reviewing platforms, public opinions are very easy to find. But when anonymity is provided, what are people really thinking?

Lucky for my inner child, I was tasked with our 18th consecutive annual Career and Salary Survey, which felt the same — if not way better — than reading through the local diner's suggestion box.

For nearly two decades, Pharma Manufacturing readers have helped us paint a landscape of the professional and emotional reality of working in the pharmaceutical industry. We've also been able to study these trends and speculate on how they reflect where the industry is headed.

While priorities and dynamics have shifted, pharma folks continue to be happy and driven by meaningful work.

Here is what changed, what stayed the same, and what we think this can tell us about the future of pharma.

### Pharma's joy remains mostly untouched

More than 89% of respondents this year said they feel satisfied within their current roles, with happiness levels ranging from 'okay' to 'very high.' According to a study led by The Conference Board, general job satisfaction in the U.S. surged to an all-time high during the pandemic, reaching almost 57% between November of 2019 and 2020.[1]

It's safe to say the pharma industry is overperforming in this department.

And it's not an easy time to be a professional in the industry either.

The responsibility to discover and develop drugs that will return the world to normalcy is unique to pharma.

But this seemingly hasn't scared anyone yet. In fact, the added pressure might be making the work more meaningful. For the past two years, challenging work had lost out to salary and benefits as the top driver of job satisfaction for our survey respondents. This year, that changed — challenging work reclaimed the throne as the top answer, with 30% of participants claiming this was the most important factor for job satisfaction.

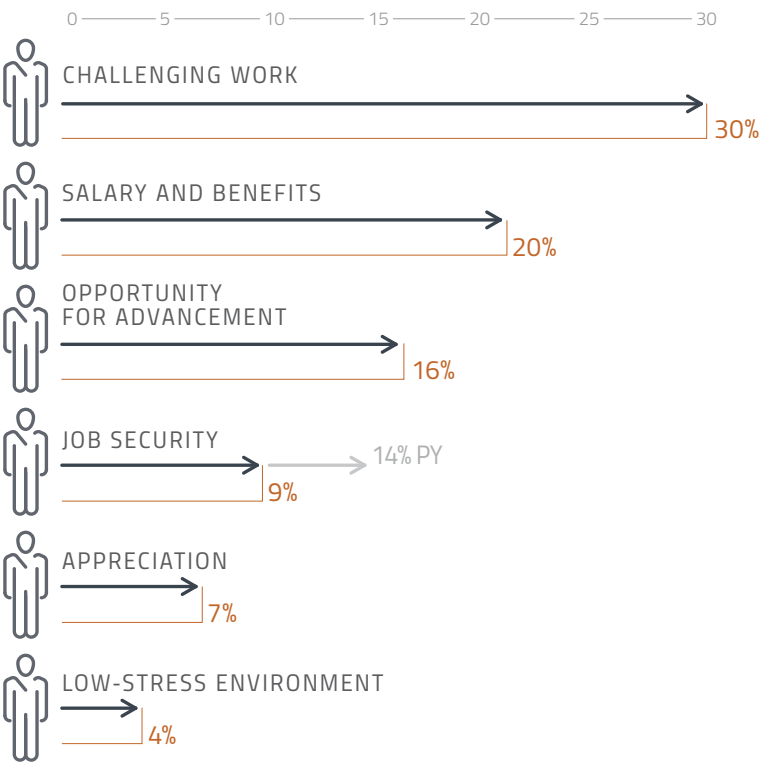
In write-in prompts, our respondents reflected this sentiment when asked what brought them the most joy about their current jobs. Respondents cited highlights such as "participating in solving of real problems" and "being challenged in what I do."

Lucky for them, there are plenty of complex problems that pharma can help mitigate.

## Let's talk money

While the last few years have brought endless challenges, the urgency to end the pandemic has also opened the money flood gates and pushed drug developers to give their best in record time.

### What is most important to you for job satisfaction?




And their best has been profitable, as the total global revenue of pharma in 2021 was $1.26 trillion.[2]

Despite the profitability of the industry, the number one concern felt by (the albeit small amount of) respondents who were concerned about job security was internal cost-cutting measures, such as potential layoffs.

This profitability doesn't seem to be reflected in salary increases either. Since 2020, there's been a steady decline in reports of raises. This year, 54% of respondents reported receiving a salary increase, down from 67% in 2019. About a third of those receiving raises reported salary increases in excess of 5%.

However, all is not lost: 62% of respondents reported receiving a bonus or additional incentive, such as extra time off or stock options.

And even though raises are in decline, pharma salaries are still highly competitive when looked at in the bigger picture. This year, 73% of our respondents reported having a gross annual salary of 80k or more, while the average earnings for full-time workers in the U.S. amount to $52K.[3]

From the data we gathered, most respondents are making more than 100k a year, with 20% making over 200k.

## Work-life balance?

Similar to professionals throughout many industries in the U.S., pharma employees are finding themselves putting in extra hours.

This year, over 85% of respondents said they're working more than a 40-hour week, rising slightly from 82% last year.

And according to the American Time Use Survey led by the U.S. Bureau of Labor Statistics, between May of 2019 and July of 2021, American workers worked an average of 4.5 hours per day and 42.5 hours per week.

On the bright side, stress levels have stayed fairly consistent over the years, with most respondents this year (just under half) saying they only feel overly stressed 'some of the time' and 19% reporting rarely or never feeling stressed.

Another continued trend the survey showed regarding work-life balance is that fewer people use all their vacation time. This year, 61% of respondents said they did not use all their 2021 PTO, compared to 56% last year. This percentage has risen steadily since 2016 when about 46% reported failing to take all allotted vacation time.

### It's an employee's world

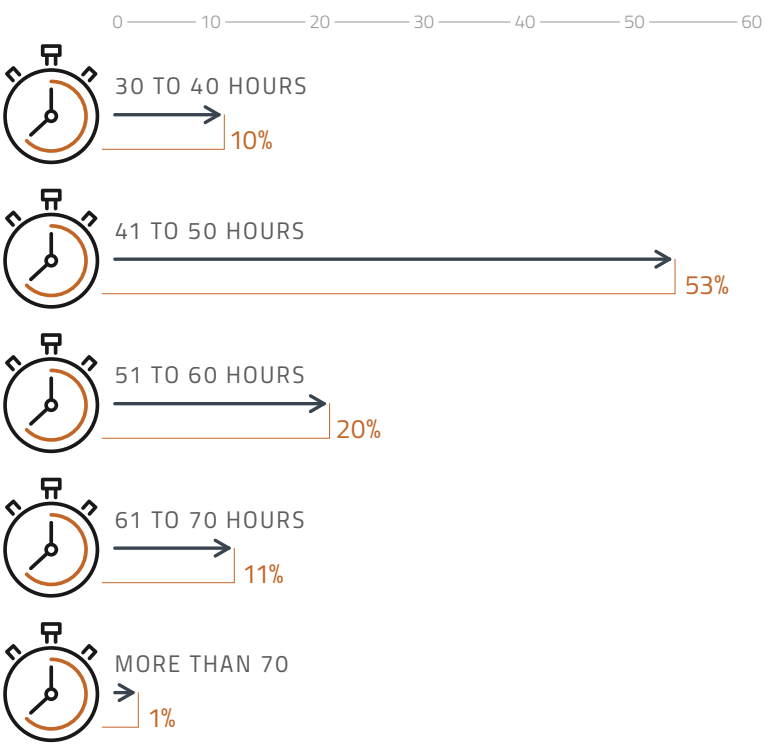
Despite how grim this picture might look, power dynamics are shifting.

Pharma professionals appear to be living in an employee market; this year, employees reported decreasing worry over job security. In fact, the importance placed on job security when it comes to job satisfaction is at an all-time low since we've been gathering responses for this question.

This year, only 9% of respondents prioritized job security over other things such as salary and benefits or opportunities for advancement.

This is not a surprise, considering we're going through what experts are calling "The Great Resignation," with people leaving their jobs in record numbers. This exodus of professionals is putting a strain on all industries, and pharma is no exception.This year, staff shortages due to resignations were the third leading cause of stress for our respondents. We've seen this is impacting the

## How many hours do you work each week?




## Survey demographics

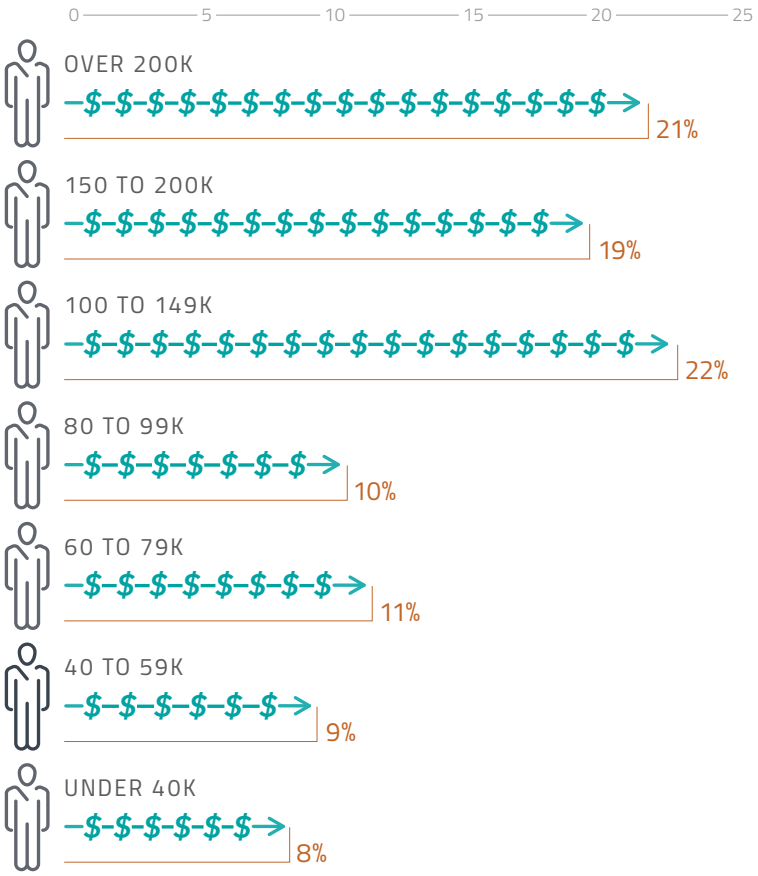
This year's study yielded 108 total responses. Participants were predominately North American-based (58%), with the remainder of respondents dispersed in Europe (14%), the Middle East and Africa (7%), Asia (11%), the Indian subcontinent (10%) and Latin America (1%).

This year, 77% of survey respondents were male, 22% female and 1% non-binary. The majority of respondents (35%) were 40 or older, with most possessing degrees in pharmaceutics, chemistry/biochemistry or biology/microbiology. About 23% work in manufacturing and operations, 18% in quality control/assessment, 8% R&D and 9% corporate management. Plant engineering, consulting, process control and regulatory functions were also represented.

Industry longevity dominated again, with an impressive 52% of total respondents boasting more than 20 years of pharma industry experience, and 86% of responding readers having seven or more years of industry experience. Of the respondents, 76% are in supervisory roles themselves, with 40% in charge of supervising five or more people.

All sectors of pharma were evenly represented, with 16% from Big Pharma, 15% from biopharmceutical manufactuers, and the same percentage of workers in generics manufacturing or small and mid-sized specialty manufacturers was reported. The remainder, including consultants, vendor/solution providers, API and excipient providers and all others, accounted for about 36% of the total.

## What is your current annual gross salary?




pharma supply chain from drug ingredient shortages to regulatory inspection challenges.

Recently, the Government Accountability Office (GAO) asked the U.S. Food and Drug Administration (FDA) to work on their international inspection backlog, which was mainly caused by a staff shortage as well.

What is causing this mass resignation? According to the World Economic Forum, industries with low location and time independence suffer the most. The organization claims that business models in which time and location proximity of employees is necessary, often fail to keep up with the digitalization of the world.[4]

Although not everyone in pharma is bailing completely — some workers have made the decision to seek new opportunities within their own companies. This year, 27% of our readers reported having a new role or position internally.

The push of the digital age could also be causing an increase in the number of workers who are concerned with skill relevance. In this year's survey, 24% of workers said that the diminishing relevance of their skills due to changing technology was the greatest threat to their job security, a staggering difference from 7% last year.

### The not-so-great stuff

Working longer hours, having unclear expectations, and increased concern over skill obsoletion were among the negative trends reported this year. Respondents also mentioned issues such as:

**Lack of feedback:** When asked if they had received meaningful feedback on job performance this year, 40% of respondents said no. "Management isn't involved enough to understand the projects and challenges but is critical when they see something they don't like," said one respondent. "Top management doesn't communicate well. They make the job more stressful," said another.

**Confusing priorities:** In some cases, busy workloads appear to be colliding with a lack of focus from the top. One respondent claimed there was "no direction and time." "No clarity of the expectation of the role," said another respondent.

**Internal struggles:** Respondents did not shy away from sharing their frustrations with internal politics and heightened stress environments, mentioning a "lack of internal support," or feeling unheard and needing to "fight to get a seat at the table." This comes as no surprise because when asked the biggest challenge faced in their current role, 38% of respondents mentioned struggles with internal management.

### Feeling good

But it's not all bad news. 60% of respondents report receiving meaningful feedback on job performance and 52% say their companies offer access to the training needed to support business goals. Pharma professionals continue to feel challenged and inspired by what they do. Other positives mentioned included:

**The people:** "I work with very smart people who work very well together. We work well together to meet our goals. Those goals move us in the direction of our mutual aim

## Biggest threats to job security

1. Internal cost-cutting measures, such as potential layoffs
2. The diminishing relevance of my skills due to changing technologies and industry focuses
3. Possible outsourcing of my position

which is ultimately to help people live better lives," said one happy respondent. Another respondent succinctly said, "The people I work with are great."

**Flexibility:** Environments that allowed for independence contributed to worker satisfaction. "I am empowered to do my work without micromanagement. I know I can go to my current manager when needed," said one respondent.

**Meaningful work:** One of the biggest takeaways this year is that pharma folks prioritize meaningful, challenging work. One respondent mentioned, "It's rewarding to make good money working well with people you like and who respect you, all while working towards something noble." For another respondent, it was "scope of work and opportunity to make an impact," that makes life in pharma enjoyable.

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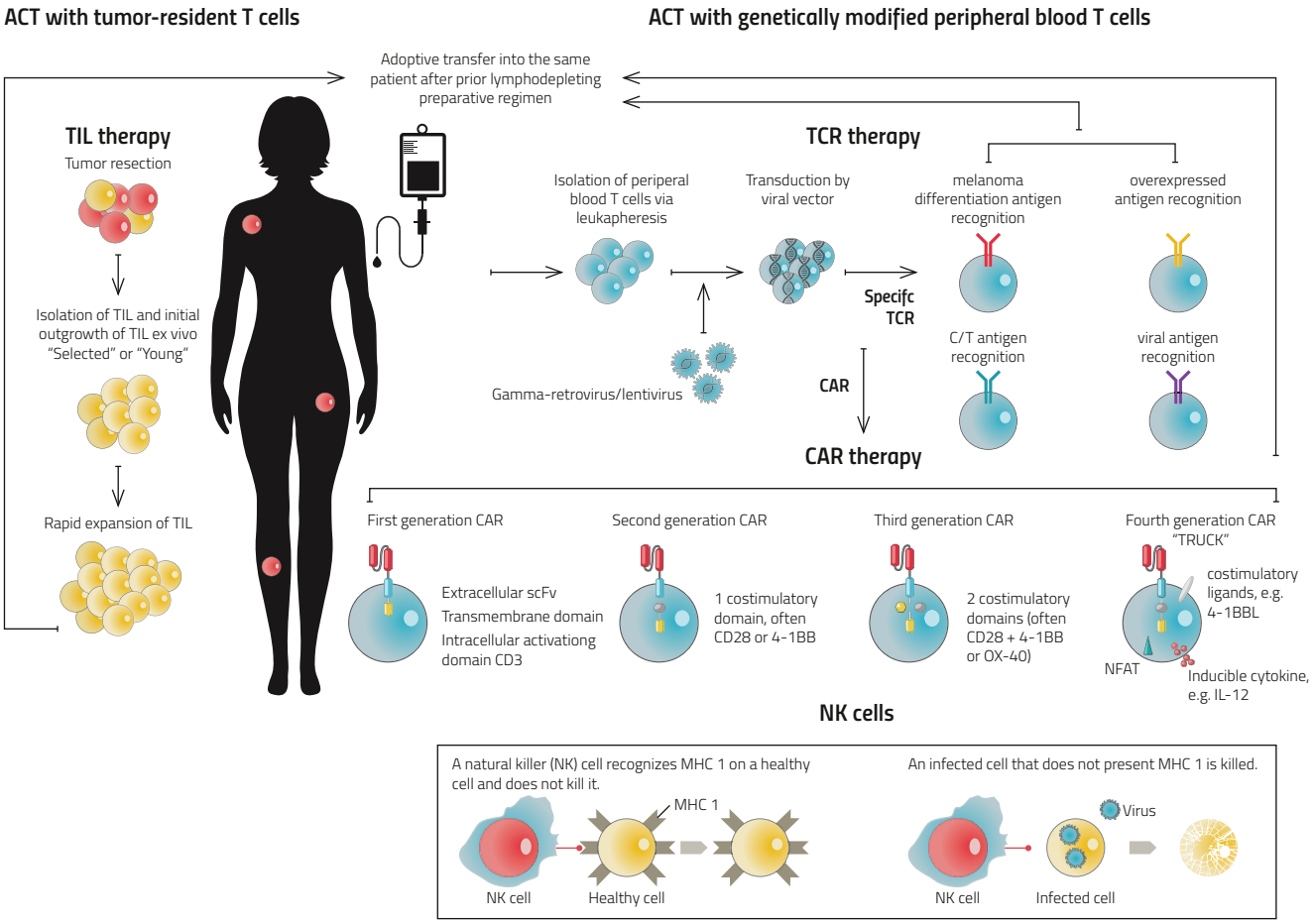
# What's next in adoptive cell therapy

## Overcoming new manufacturing challenges as the cellular immunotherapy landscape expands

Biopharma manufacturers know that adoptive cell therapies (ACTs) such as chimeric antigen receptor (CAR) T-cell therapies are unlike anything that has come before.

ACTs are living drugs. Specifically, they're human cells that, when modified or expanded, gain efficacy in the treatment of cancer. CAR T-cells in particular have shown unprecedented success in the clinic and they are bound to bring much-needed relief to thousands of people with cancer in the years to come. However, increasing demand for ACTs will come with a critical need for a new approach to biopharmaceutical manufacturing. Unlike small molecule and protein-based drugs, whose discovery process is relatively standardized and whose manufacture is stoichiometrically predictable, ACT development and manufacturing involves multiple layers of variability and complexity.

CAR T-cells have progressed far into the clinic despite these manufacturing limitations: Patients in the U.S. with different types of blood cancer can receive CAR T-cell therapy in over 150 treatment




centers in 38 states and the District of Columbia. The fact that CAR T-cells reached the clinic at all is a feat of biomedical engineering.[1] Still, CAR T-cells are not the end of the story for ACT development. Several other types of ACT are under investigation and in the next decade or so, CAR T-cells might find company in their space.

Other ACTs on their way to the clinic include T-cell receptor (TCR) T-cell therapies, tumor-infiltrating lymphocytes (TILs) and natural killer (NK) cells. This burgeoning pipeline offers hope to people with cancer who do not have access to safe and effective treatments.

The growing popularity of ACTs also cements the reality that the manufacturing process for cancer treatments will never be the same. This article will explore the manufacturing challenges that still impact CAR T-cell developers and the hurdles that developers must still overcome as other types of ACTs speed towards clinical use.

## CAR-T manufacturing challenges

CAR T-cells are custom-designed and specially constructed immune cells that selectively target tumor cells for destruction. T-cells normally kill foreign invaders in the body, but tumor cells typically evade the body's defenses and grow unrestrained. By transfecting T-cells with the gene for the CAR protein, T-cells can be trained to identify cancer and destroy it as if it were any other foreign invader.

Today's CAR T-cells are autologous, meaning that each therapy is derived from an individual patient's blood. After a patient has their blood drawn, the samples are sent to a CAR T-cell manufacturer, where the manufacturer isolates the T-cells and engineers them to express the CAR gene using a virus or transposon system. The cells are then expanded and returned to the clinic, where a physician reinfuses the cells into the patient's bloodstream.

These cells' autologous nature creates benefits and drawbacks for both patients and manufacturers. Since the cells come from a patient's own body, the chances of eliciting an adverse immune reaction based on incompatibility are slim. On the downside, autologous CAR T-cell production is slow; it can take several weeks for the treatment to arrive at the clinic. Several steps

must take place before manufacturing can begin: The patient must be diagnosed, a physician must decide to pursue CAR T-cell therapy, and the patient's blood must be drawn and sent to the lab. Only then can the manufacturer engineer the cells to treat cancer. Every day that a patient must wait for the treatment to arrive is one less day of receiving a treatment that may save their life.

Biopharmaceutical companies are actively seeking ways to develop allogeneic CAR T-cells. These cells could drastically reduce wait times by offering a standardized, off-the-shelf treatment option. However, since these cells are foreign to the body, they pose additional risks. For example, the patient's immune system may kill the cells before they have any therapeutic benefit, or worse, the infusion can cause graft-vs-host disease, where the CAR T-cells attack healthy tissue.

Regardless of their source, CAR T-cells pose several manufacturing challenges. Since their development cannot be completely controlled, the safety and efficacy of any single batch cannot be guaranteed. For example, when introducing the CAR gene to T-cells, the transfection step is not perfectly efficient. Some cells may not accept the transgene and never become CAR T-cells. On the other hand, too many copies of the transgene may integrate into each genome, posing a potential safety issue.

If a cell contains more than four copies of the transgene, the cell can become toxic and cause an inflammatory response that leads to organ dysfunction and death.[2] Consequently, if a batch contains this many copies per cell, the Food and Drug Administration recommends that manufacturers screen it out.[3] Finally, some viral vectors used for transfection may make it through the filter steps and end up in the final batch. If these viruses are replication-competent, they could theoretically cause the growth of T-cell neoplasms, another form of cancer. For these reasons and more, manufacturers need to use quality control methods to screen out suboptimal batches before they reach patients.

Fortunately, the tools and techniques needed to monitor the quality of CAR T-cell therapies already exist. Techniques such as flow cytometry and Droplet Digital PCR (ddPCR) can be used to monitor transfection efficiency, CAR-T copy number and the presence of replication-competent viruses and other contaminants.

Currently, researchers are developing novel CAR T-cell therapies, as well as other ACTs, that overcome several of these limitations.

**The growing popularity of ACTs cements the reality that the manufacturing process for cancer treatments will never be the same.**

## Treating solid tumors with TCR T-cells

One drawback of CAR T-cells is their low efficacy in treating cancers beyond those circulating through the blood. These cells are limited by their relative inability to infiltrate solid tumors (such as those found in breast or prostate tissue). But T-cell receptor T-cells may help solve this challenge.

Like CAR T-cell therapy, TCR therapy involves genetically modifying T-cells to express a protein that targets tumor cells. But unlike CAR T-cells, which only target cells that express certain cell surface proteins, TCRs can direct T-cells towards any antigen, whether it is expressed on the surface of a tumor cell or internally.[4] A fragment of that antigen simply needs to be presented by a tumor cell's major histocompatibility complex (MHC).

MHCs are protein structures that help T-cells differentiate between types of cells. TCRs recognize the MHCs on tumor cells as foreign and then signal T-cells to destroy the cells. In other words, TCR T-cells amplify the adaptive immune response to tumor cells. Since TCR T-cells can identify foreign cells by their intracellular antigens, they could potentially be effective in treating solid tumors.

TCR T-cell manufacturing poses similar challenges to CAR T-cell manufacturing. Manufacturers must still be careful to monitor cells for transfection efficiency and copy number, as well as the presence of harmful contaminants. Also, like today's CAR T-cells, the TCR T-cells currently under development are autologous and therefore take weeks to manufacture, creating similar delays and risks for patients. An allogeneic TCR T-cell could theoretically reduce wait times and increase the efficacy of this promising therapy.

## Boosting innate immune activity with TILs

A tumor-infiltrating lymphocyte (TIL) is any T-cell or B-cell that has successfully entered a tumor mass. These cells' unique ability to infiltrate solid tumors gives them immense therapeutic potential. It also tells us a lot about how these cells could function in the clinic.

For instance, TILs naturally recognize tumor antigens and do not need to be genetically modified. Rather, to be used as an autologous therapy, they merely need to be made stronger. This involves taking a blood sample, isolating and expanding the TIL cells and returning them to the patient.

No TILs have achieved FDA approval yet, but it is neither safety nor effectiveness concerns that have held them back. Rather, it is the challenge of manufacturing them at scale. The manufacturing process for TILs is complex, requiring technical skill and six to eight weeks to accomplish. First, the TILs can only be harvested from tumor tissue, which means a patient must undergo an invasive tissue biopsy. Then, the tissue gets dissected in the lab, and scientists plate the cells and employ a multifaceted digestion process to isolate the lymphocytes. Finally, the cells get expanded and returned to the patient for treatment. The complexity of this protocol makes it challenging to implement the therapy in the clinic.

As TCR T-cells, TILs and NK cells reach the approval stage, they may all one day offer hope to patients with a wider variety of cancers.

## NK cells: A different kind of lymphocyte

Not all ACTs rely upon T-cell activity. For example, natural killer cells are another type of lymphocyte that evolved specifically to attack tumor cells. These cells' unique mechanism of action gives them potential in the clinic and might make the manufacturing process simpler and cheaper.

When NK cells identify a tumor cell, they attack the tumor and release chemical signals that activate the adaptive immune system against it. Since these cells seek out tumor cells on their own, they do not need to be genetically modified to be used as cancer therapy, making the discovery and manufacturing process much simpler.

NK cells are considered safe, even when they are allogeneic.[5] This characteristic makes them a suitable source of off-the-shelf ACTs. With this flexibility, manufacturers can save time and money by manufacturing larger batches. This

pays off for patients, as well, who will not have to wait weeks to receive ACT.

Despite their natural tendency to attack tumors, NK cells cannot overcome tumors without help because the tumor microenvironment suppresses their activity.[6] Here, the CAR protein may be able to help. Engineering NK cells to express the CAR protein may boost their activity and help them overcome the immunosuppressive behavior of tumor cells.

NK cell manufacturing is not without its challenges. NK cells are difficult to expand in vitro. Also, in most cases, NK cells do not infiltrate solid tumors, limiting their potential in treating cancers beyond blood cancer. However, as a treatment for leukemia and lymphoma, NK cells promise a more effective, easier-to-produce ACT option.

## Adoptive cell therapy's next act

The FDA approval of CAR T-cell therapy was only the beginning for ACTs. As TCR T-cells, TILs and NK cells reach the approval stage, they may all one day offer hope to patients with a wider variety of cancers.

As manufacturers aim to produce safe and effective therapies quickly and inexpensively, all of these therapies will create new challenges. But biomanufacturers do not have to face these challenges alone: regulators believe in these therapies so much that the FDA has published several guidances aimed at helping biomanufacturers improve their ACT manufacturing practices.

With support from regulators and unrelenting demand from patients and physicians, biomanufacturers will hopefully discover new ways to make ACT manufacturing more efficient so more treatments can reach more patients while they can still make a difference.

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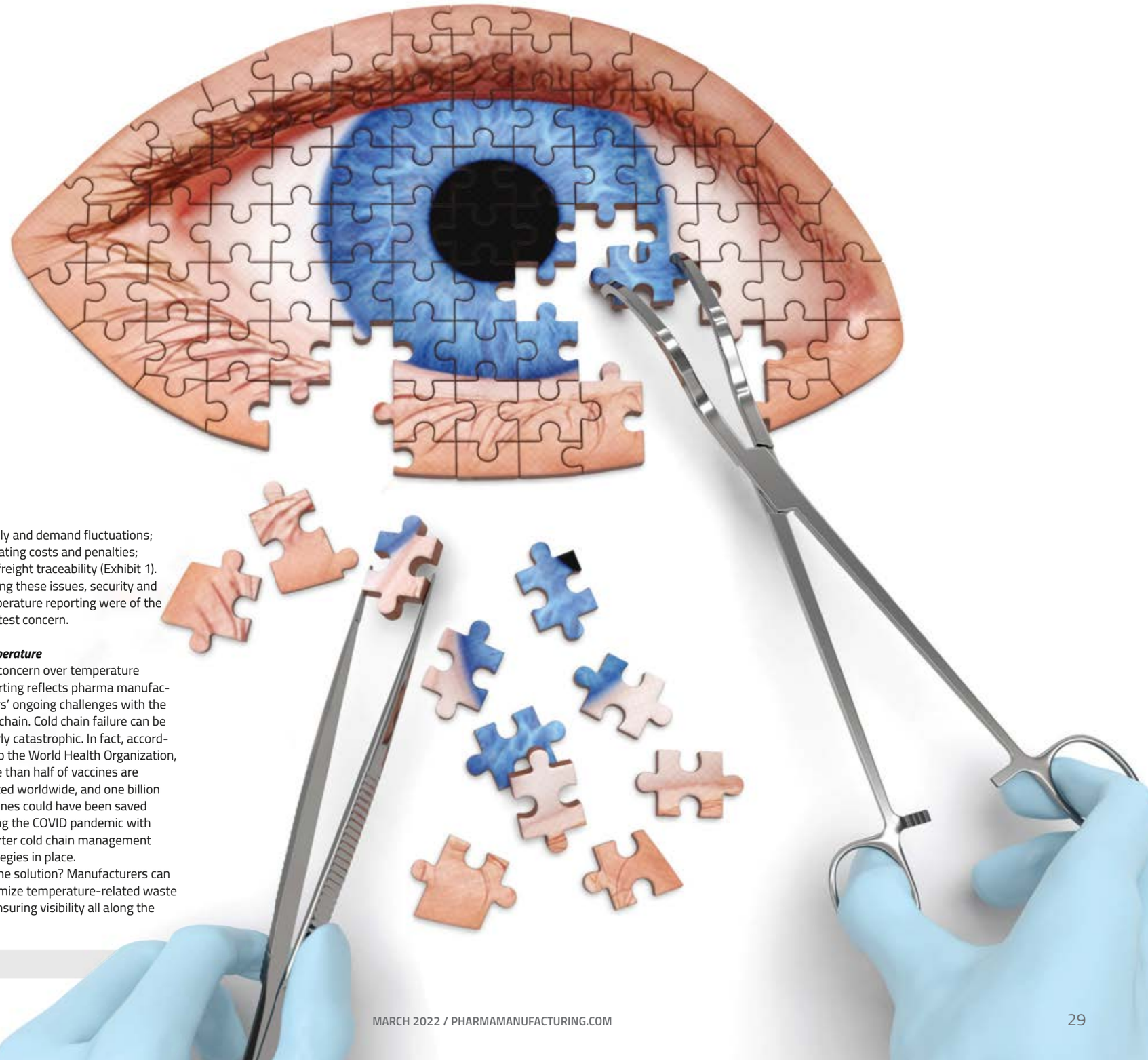
# Closing the visibility gap

## A proactive approach can help pharma realize the promise of end-to-end visibility over supply chain networks



The COVID-19 pandemic has tested the resilience of institutions, processes and systems across all industries and geographies, including the pharmaceutical supply chain. Escalating cold chain supply challenges, paired with increasing consumer pressures, have highlighted the urgent need for visibility at every node along the chain.

A recent FourKites industry survey* on the state of the pharma supply chain explored the current lack of visibility and the accelerated industry need for predictability and control across the pharma supply chain — confirming that these issues are more important than ever before for pharma manufacturers. In these areas, smarter supply chain visibility can help manufacturers take a more strategic, proactive approach — an important step towards the goal of end-to-end supply chain visibility and control.

### Transport and storage

Pharma manufacturers are feeling serious pressure all along the supply chain. In many cases, they are accountable for a vaccine or therapy until the point of patient vaccination. That means manufacturers own the product even after it enters a health care facility, up until the very moment it's administered to the patient. This translates to several potential vulnerabilities that must be considered.

Respondents to the FourKites survey reported four major pain points in transporting and storing goods: product protection and the need to quarantine; supply and demand fluctuations; operating costs and penalties; and freight traceability (Exhibit 1). Among these issues, security and temperature reporting were of the greatest concern.

***Temperature***

The concern over temperature reporting reflects pharma manufacturers' ongoing challenges with the cold chain. Cold chain failure can be utterly catastrophic. In fact, according to the World Health Organization, more than half of vaccines are wasted worldwide, and one billion vaccines could have been saved during the COVID pandemic with smarter cold chain management strategies in place.

The solution? Manufacturers can minimize temperature-related waste by ensuring visibility all along the

* "The Pharmaceutical Supply Chain: Closing the Visibility Gap" survey and report includes findings from 100 supply chain companies across the United States.

path of storage and shipping, as well as adequate windows to intervene when necessary. A well-rounded supply chain visibility (SCV) solution will include numerous failsafe technologies, such as temperature monitors, temperature trend analysis and real-time alerts. With the ability to connect with carriers and locations to alert them if conditions are falling outside parameters and compliance, manufacturers can protect these lifesaving medicines — as well as their bottom lines.

***Security***

Another peril that has historically challenged pharma manufacturers is product theft. Almost one-third of the FourKites survey respondents identified product protection as their biggest pain point in transporting and storing pharmaceuticals. Their concerns are not unfounded; the United States ranks in the top three countries for pharmaceutical cargo theft. In 2020, $1.2 million in oncology drugs were stolen from cold storage at a warehouse in a single theft. Besides facility break-ins, truckload thefts also occur.

Manufacturers have long implemented security measures to protect against theft. Nearly all (96%) of the survey respondents pinpointed security reports as their main approach to promoting product retention — outranking both temperature and regulatory reporting. Organizations also use physical security practices as guardrails, including hiring third-party security services, deploying decoy shipments, and even banning vehicle stops within the first and last 250 miles of a shipment, where the risk for theft is greatest.

However, manufacturers concerned about product loss should also consider newer, 'smarter' solutions. IoT-based sensor tracking complements physical security, engaging real-time data and alerts to provide greater insight into product security and status. With physical

**Smarter supply chain visibility can help pharma manufacturers move away from the Just-In-Time model to a more strategic, proactive approach.**

location tracking of every shipment, around the clock, manufacturers can receive alerts when a truck stops or goes off-route and can pinpoint the truck's diverted location. Some platforms also define spots where issues are most likely to occur and can alert manufacturers when a load is approaching a high-risk area.

## Inbound and outbound challenges

Pharma manufacturers must contend with several inbound and outbound supply chain challenges, ranging from yard management to accurate ETAs.

The most pressing inbound challenges include supplier manufacturing visibility, supplier compliance, visibility of product in-transit and its ETA, and the purchasing process (Exhibit 2).

Outbound challenges cited by respondents also included visibility and ETAs, as well as carrier availability, temperature monitoring, coordination of delivery windows, and security compliance.

Pharma manufacturers can address many of these inbound and outbound challenges through end-to-end visibility solutions.

Predictive ETAs are an essential piece of the puzzle. By pinpointing the exact location of shipments, predictive ETAs can save manufacturers time and resources while helping them avoid costly expediting measures. This open view into product shipments, across modes and continents, results in greater efficiency and prevents the bullwhip effect — increasing swings in inventory in response to shifts in consumer demand as one moves further up the supply chain. With the ability to calculate accurate cycle timing, organizations can right-size inventory — actively mitigating risk and reducing costs.

EXHIBIT 1

### Biggest pain point in transporting/storing goods

Nearly a third of the executives surveyed identified product protection as their most demanding storage and transportation challenge.

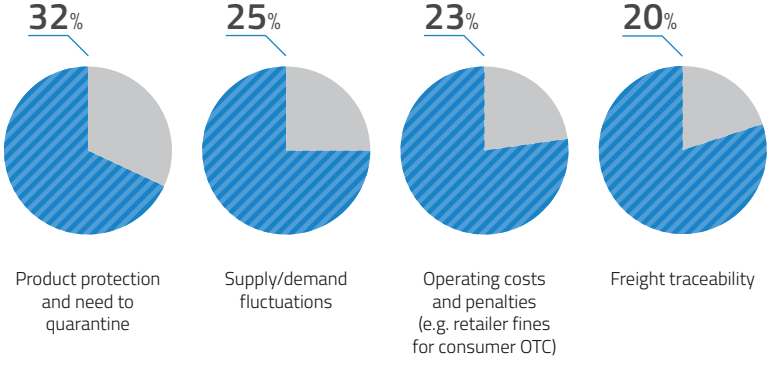
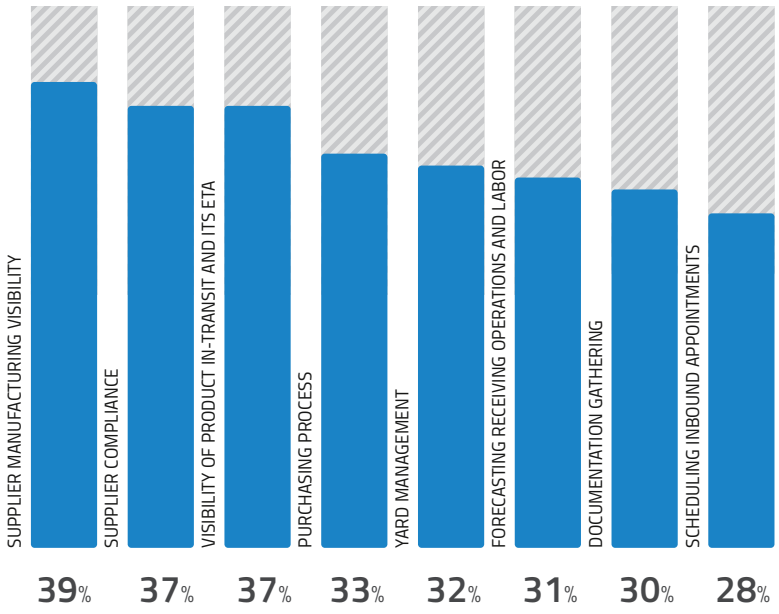


EXHIBIT 2

## Most pressing inbound challenges

Supplier manufacturing visibility, supplier compliance, and product ETA and visibility in transit topped the list of inbound supply chain challenges.




Advanced yard management systems can also protect manufacturers' bottom line. Unlike traditional yard management solutions, which only show manufacturers what's currently in their yard, today's technology leverages real-time visibility of in-transit and in-yard freight to give manufacturers even more flexibility and insights.

Advanced solutions can help yard managers in many other areas, including workflow automation, SKU-level inventory visibility and the ability to dynamically change appointment schedules based on actual arrival times.

### The next level: big-picture thinking

In all areas, smarter supply chain visibility can help pharma manufacturers move away from the Just-In-Time model to a more strategic, proactive approach. However, pharma must adopt big picture thinking to fully realize the promise of end-to-end visibility and control over complex supply chain networks.

***The control tower***

The control tower concept refers to the effort to stitch together complex and siloed supply chains, so organizations have greater visibility and better insights, resulting in more efficient operations. While survey respondents expect to invest in artificial intelligence, advanced analytics and various digital supply chain technologies in the coming months and years, the report predicts that less than 5% of control tower-like deployments will fulfill their end-to-end potential.

Real-time visibility platforms are an essential piece to complete this puzzle. We estimate that, by 2023, 50% of global product-centric enterprises will have invested in real-time visibility platforms. These solutions will help manufacturers predict the future of their supply chains, rather than simply reacting to disruptions as they occur.

***Ongoing collaboration and education***

The past two years have taught us that change is constant. While our modern diversity of medications, treatment options and access to health care facilities, including telemedicine, has been incredibly positive for patients, it has also resulted in serious challenges for the unprepared pharmaceutical supply chain. The pharmaceutical logistics market is growing more complicated, with a surge in cutting-edge treatments actively in development, and obstacles and product loss increasing with cold chain requirements.

To keep up, the pharma industry must embrace change through continuous collaboration and education. When choosing a supply chain visibility platform, manufacturers and shippers alike should consider longevity: Will this service help us stay on top of ever-evolving technologies? Will it help us continually train our employees on the latest updates? Will it connect us with the greater logistics community, providing us access to real-time and real-world insights? An all-inclusive visibility platform will help your organization maximize its supply chain not just for today, but also into the foreseeable future.

The FourKites survey confirmed what many in the industry already recognize: Visibility, predictability, and control across the pharma supply chain are more important now than ever before. In the face of mounting patient pressures and unprecedented environmental disruptions, now is the time for innovation. Real-time visibility, through an end-to-end supply chain visibility platform, will help pharma manufacturers rise to the challenge, through the pandemic and beyond.

**Mike Hook**
Sales & Marketing Director, PRAB

# Upping your wastewater treatment game

## A better wastewater management strategy can lead to lower risk exposure and costs

Without question, water consumption is becoming an area of increasing focus for pharmaceutical manufacturers who wish to be both responsible corporate citizens and profitable as a business.

With water costs on the rise and the gap between global water supply and demand projected to reach 40% by 2030 if current practices continue, water usage in pharmaceutical product development not only contributes to the global water supply shortage, it also elevates risk at the corporate level.[1]

According to a report from the U.S. Department of Energy, the average annual price escalation rate for water is 4.1% based on reported rates from 2008 through 2016.[2] In addition to the cost of raw materials, wastewater compliance costs are mounting. Several factors contribute to higher water expenses, such as sewer fees for discharge to a wastewater treatment plant, sewer permits for effluent, biological oxygen demand, chemical oxygen demand and fines for overages.

Both reputation and operational sustainability are at stake. Fortunately, as pharma companies hone environmental, social and corporate governance strategies, sustainability improvements — specifically in wastewater management — are helping these entities demonstrate responsible operating practices that benefit both the global community and the bottom line.

## Treatment goals

To combat rising costs and meet compliance directives, many pharma companies are adopting Zero Liquid Discharge (ZLD) programs that minimize or eliminate the discharge of effluent by treating and recycling wastewater. ZLD is achieved by removing contaminants from wastewater to produce a distillate that may be reused, resulting in zero discharge at the conclusion of the treatment cycle.

Wastewater treatment systems allow pharma manufacturers to decrease their water expenses, meet ZLD goals and comply with state and local regulations. Disposal costs can drop as low as 15 times the original amount. With capabilities that are proven to not only reduce water consumption but also lower carbon dioxide emissions, wastewater recycling equipment is progressively becoming a part of pharma sustainability action plans. Overall, these treatment systems are capable of reducing water volumes up to 98%.

For instance, a research laboratory center developing therapeutic products to help with respiratory, musculoskeletal and cardiovascular diseases was consuming high quantities of water in its processes. During a typical day, the lab discharged about 4-tons of effluent, resulting in a high volume of wastewater and disposal costs. If the pharma lab treated the wastewater and reused the treated water in its processes, water consumption and disposal costs would decrease substantially. By adding vacuum evaporation to treat its wastewater, the facility was able to recover more than 90% of the water for reuse.[3]

## On-site challenges

While pharma manufacturers have much to gain from wastewater treatment, adding these capabilities on-site is not without challenges. Pharmaceutical wastewater treatment is a particularly specialized process because the wastewaters are highly inconsistent. Whether producing APIs or finished products via chemical synthesis or bioprocessing, each wastewater is derivative of the unique processes used to develop the product. Plants producing the same product can have variations in the wastewater. As a result, wastewater treatment systems are equally diverse.

Laboratory analysis of the wastewater, a careful review of the production process and a goal assessment provides a starting point for specifying a treatment solution. During the review, water volumes, water temperature and flow rates all need to be defined. Additionally, operational goals need to be discussed. For a treatment plan that includes reuse, parameters of the recycled water are dependent on the reuse application. In most cases, reuse applications are for low-grade water requirements such as makeup water for cooling towers, boilers, cleaning or irrigation.

Parameters that are analyzed during laboratory testing include:

- pH
- chemical oxygen demand (COD)
- biological oxygen demand (BOD)
- total suspended solids (TSS)
- total kjeldahl nitrogen (TKN)
- ammonia (N-NH4+)

- total phosphorus (TP)
- fat, oil and grease (FOG)
- total dissolved solids (TDS)
- salts
- microorganisms

Lab analysis results will help wastewater treatment experts define a system that will perform the processes needed to meet compliance and business objectives. There are several key processes used to treat pharmaceutical wastewaters. They include:

**Segregating or deactivating wastewater streams:** This may be necessary to treat highly concentrated or toxic streams, or it may be more cost-effective in cases where the bulk of wastewater does not contain APIs and, therefore, treating the full volume of the wastewater for API reduction/removal is inefficient. Streams containing biologically active ingredients may need to deactivate those substances before being combined with other wastewater streams.

**Equalization:** Placing wastewater in an equalization tank equalizes the flow rate, balances the contaminants and eliminates temperature fluctuation.

**pH adjustment:** Adjusting the alkalinity or acidity of wastewater may be needed to achieve efficient processing in downstream treatment stages.

**Removing suspended solids:** This may be achieved through a combination of coagulation, which clumps particles together, flocculation, which removes the clumps, flotation, sedimentation or filtration.

**Aerobic or anaerobic biological treatment:** This converts biodegradable organic matter into biomass that may then be separated from the treated water.

**Evaporation:** Also known as evapoconcentration or distillation, this process is used to reduce the volume of wastewater before disposal. It produces high-quality condensate that in many cases may be recycled and reused.

**Sustainability improvements are helping pharma companies demonstrate responsible operating practices that benefit both the global community and the bottom line.**

## Types of wastewater treatment systems

Because treatment of pharmaceutical wastewater is unique to the production process, modular wastewater treatment solutions are needed to complete specific treatment processes. Here are four common solutions that pharma manufacturers are using to lower costs and meet sustainability goals:

**Oil water separators:** These systems can reduce haul-away costs up to 90%, decrease water consumption, and increase the lifespan of soluble oils, wash water, rinse water and pressure wash-down water (or process water). A down-flow gravity coalescing method separates oil from water to less than 15 ppm. The oil/water mixture is pumped via a floating skimmer or is gravity fed into a separator, where free and mechanically dispersed oil is removed from the influent. The separated oil is automatically gravity discharged to a waste container. The clean water is discharged by gravity or through an optional discharge pump to the sewer, or back into the process.

**Ultrafiltration (UF):** These systems clarify solutions containing suspended solids, bacteria, and high concentrations of macromolecules, including oil and water. Ultrafiltration utilizes crossflow filtration to remove emulsified oils, suspended solids, metal hydroxides, emulsions, dispersed material, suspended solids, and other large molecular weight materials.

During UF, fluid flows parallel to a semi-permeable membrane, which retains the emulsified oils and the suspended solids, while the water and dissolved solids pass through the membrane. Different membrane configurations help pharma companies accommodate unique operational considerations such as floor space and energy consumption.

Additionally, the quality of the effluent that UF produces is typically very consistent. This dependability reduces the amount of testing required to validate the quality of the water for reuse.

**Vacuum evaporation**: Evaporation differentiates itself from other separation processes by removing water from contaminants, as opposed to filtering contaminants from the water. Vacuum evaporators achieve the highest rates of water recovery and concentration. Capable of treating and distilling pharmaceutical wastewater volumes from 1 to 120 tons per day and producing residual total solids concentrations of more than 85%, vacuum evaporators can reduce water costs up to 99%. Three types of vacuum evaporators include:

- Heat pumps: Flexible and versatile with low electrical energy consumption and superior reliability
- Hot water/cold water: Utilizes existing excess hot water/steam and cooling water to lower operating costs
- Mechanical Vapor Recompression (MVR): Uses low boiling temperatures to treat wastewater volumes with high flow rates

**Reverse osmosis (RO):** This filtration technology removes dissolved solids and impurities from water using a semi-permeable membrane. The membrane

allows the passage of water but retains the majority of dissolved solids and other contaminants. An RO system that is properly designed and operated can remove up to 99.5% of incoming dissolved salts and impurities. However, RO membranes require high water pressure (greater than osmotic pressure) to work effectively.

## Extending risk management beyond the plant

Although pharma companies should first look at water usage in their operations, supply chain sources also merit scrutiny. An estimated 80% of the world's APIs come from China, India and a few other foreign countries.[4] Because water insecurity is a global concern, risk management must extend beyond the walls of a company's manufacturing plant — especially as drug developers intensify production efforts to meet the growing demand for pharmaceuticals.

According to a report from Barclays, the cost for biotech, healthcare and pharma industries to address water usage is $4 billion, compared to the $52 billion potential maximum financial impact the industries could face if they fail to address water insecurity.[5] Drug producers that utilize on-site wastewater treatment and recycling will simultaneously advance their sustainability practices, safeguard the pharmaceutical supply and develop a competitive advantage.

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1 | *World Economic Forum. We're helping to close the gap between global water demand and supply. (2021).*

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# Wastewater sources and processes

Not only is water a fundamental excipient in pharmaceutical development, but it is also essential for numerous processes used to support production. Generators of wastewater in pharma manufacturing include:

**Chemical reactors:** Wastewater is produced with each chemical modification as reactors are emptied, cleaned and refilled. The wastewater may include reaction residues, unreacted reactants, products and byproducts, including acids, bases, metals, halides, nitrates, cyanides, sulfates and API traces.

**Fermentation and purification processes:** The wastewater may include biologically active substances (such as enzymes), nutrients (starches, sugars, polyols), trace elements, vitamins, amino acids, inorganic and organic salts, surface active agents or complex (undefined) ingredients.

**Extraction processes:** More than 30 solvents are regularly used in pharmaceutical manufacturing including ethanol, methanol, acetone, isopropanol and acetic acid. Although some solvents are recovered before discharge, a portion remains in the plants' wastewater.

**Mixing and granulation processes:** Wastewater is produced after equipment used to mix APIs and excipients is rinsed. The wastewater may contain residues from detergents, excipients and APIs, such as waste starches and sugars.

**Equipment and floor cleaning:** Wastewater contains detergents and pollutants resulting from equipment utilization.

**Scrubber blowdown:** Wastewater produced from scrubber blowdowns contain soluble and insoluble organic compounds and absorbed chemicals (acids/bases).

**Laboratory facilities:** Wastewater from laboratory facilities may include toxic compounds and traces of APIs.

**Production of compendial and utility waters:** Examples of this include reverse osmosis concentrates and cooling tower/boiler blowdown wastewaters, which contain dissolved salts, alkalinity, clean-in-place chemicals and total suspended solids.

**Sanitary wastewater:** This wastewater may contain organic pollutants, suspended solids, fat, oil and grease (FOG), and microorganisms. If wastewater is to be treated and reused, sanitary wastewater should not be combined with other wastewaters intended for reuse.

SOURCE: VEOLIA, PHARMACEUTICAL MANUFACTURING—WASTEWATER TREATMENT GUIDE.

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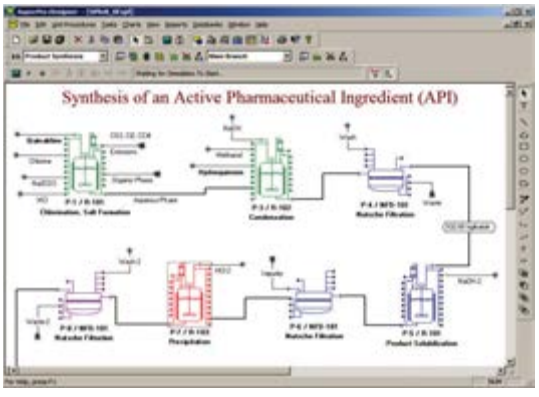


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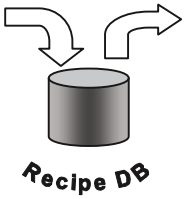


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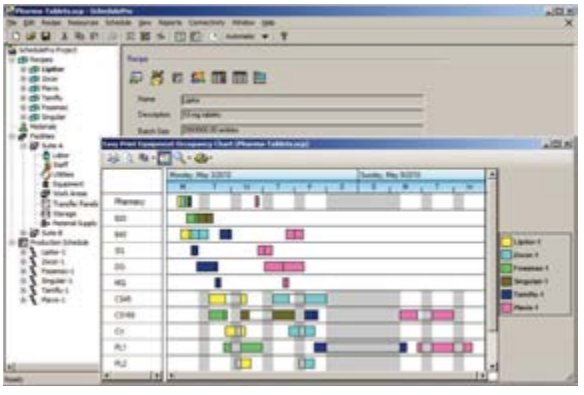

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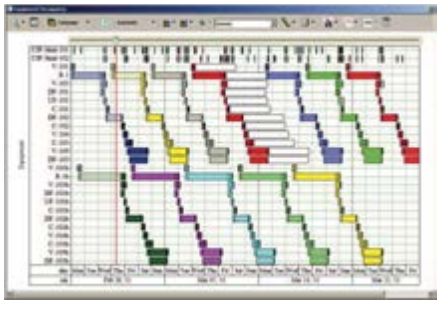

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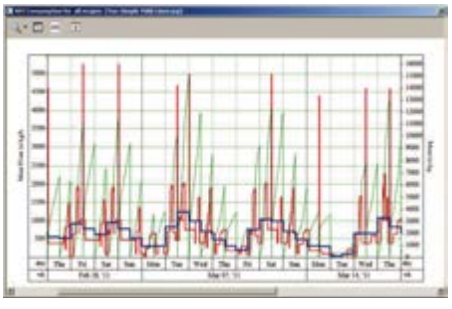

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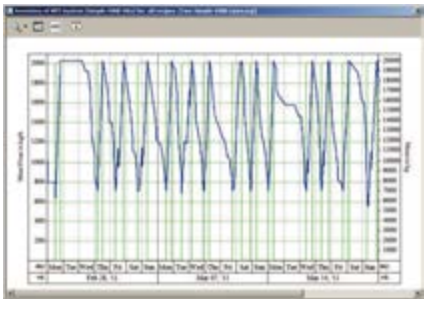

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**SchedulePro** is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, 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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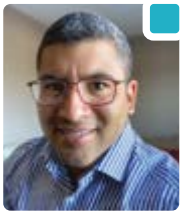

# The marathoner approach to OEE

Encouraging better site performance through attainable, progressive improvements can help teams accept best practices

A few years back, I had the opportunity to work with a pharmaceutical company looking to improve overall equipment effectiveness (OEE) across all of its global manufacturing facilities. The organization had many challenges, including personnel issues and a lack of training, as well as the fact that operational performance was not consistent across facilities.

Inspired by these challenges, the company wanted to have more visibility into the performance of its operations. That called to mind the need for a maintenance execution system (MES), delay accounting and a downtime tracking solution.

What typically happens after a company identifies the need for more visibility is a benchmarking exercise. As organizations look to tackle new initiatives, they compare the performance of facilities against worldwide standards. This comparison usually takes place before an organization is in the right place to execute consistently and match these key performance metrics. It assumes that a target, once identified and established, can be reached. The story on the ground can feel a world apart.

## Finding the right pace

After listening to the different teams spread across the pharma company's various facilities, we ultimately recommended that they design an approach that would help them improve over time. This gradual method contrasts with setting a performance goal that tracks against a target, like an objective to reach 85% of industry best practices for yield quality or material waste.

On the floor, the change in mentality that comes as a result of following a progressive approach is noticeably different from the blanket approach to best practices. The gradual approach removes the feeling of punishment or shame for underperforming benchmarks. It also keeps counterproductive practices in check, like overproducing to make up for low demand periods.

Encouraging better site performance through tangible, attainable improvements goes a long way toward helping teams to accept best practices. It is their success, after all, that is also the success of an individual site.

We eventually called this method the marathoner approach to Key Performance Indicators (KPIs) and OEE. The name came about after I watched a friend prepare for a marathon. She started with a set time for 1K and then established attainable goals at different distances (2K, 5K) that motivated her to cut time off her pace and get better. Once she found the right pace, it was easier for her to make progress on her next challenges at 10K and 20K.

OEE is a model metric for the marathoner approach because it is recorded as a percentage of quality, throughput and availability. An organization can define its targets incrementally as well as the steps it takes to get to each one.

Obviously, any organization would like to maximize capacity, but it takes time to raise the profile of a site. For this specific pharma customer, we established a sustainable baseline rate that would produce good quality products.

We level-set their OEE target (1K) so they could meet their targets consistently. That gave the site time to find its pace. This target, once achieved, also showed them they could get better. Their own progress, and the challenge that prompted the initiative, could be more easily acknowledged. It allowed them to find ways to understand where production bottlenecks were and the steps required to improve their processes, people, and even technology that would help them unlock the next levels of OEE (2K, 5K, 10K, 20K).

## Taking the right approach

This is just one example of how a change management approach can be incorporated into a new system implementation. The approach establishes a data-driven method to help organizations measure performance and considers current operational conditions (work culture, personnel skills, equipment health, maintenance practices).

And, importantly, it introduces a positive approach to motivate people to get better over the course of time. All that is to say, the right tool is also the one the culture runs with.

As part of that operationalization, pharma organizations can integrate and align this marathoner approach with overall manufacturing excellence programs.

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