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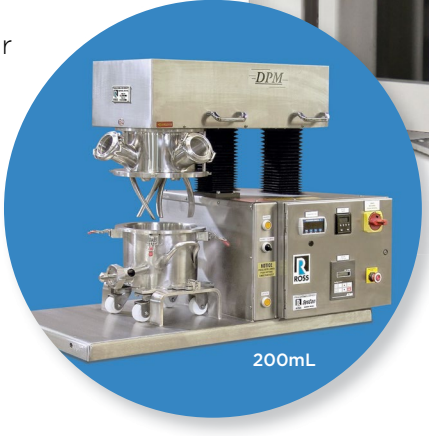

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On the cover

COVER STORY

16 Public Opinion: Can Pharma Chart a New Course?

As the high cost of drugs continues to erode public opinion, experts ask whether price controls are the best, or only, way to improve access to medicines and regain the public's trust.

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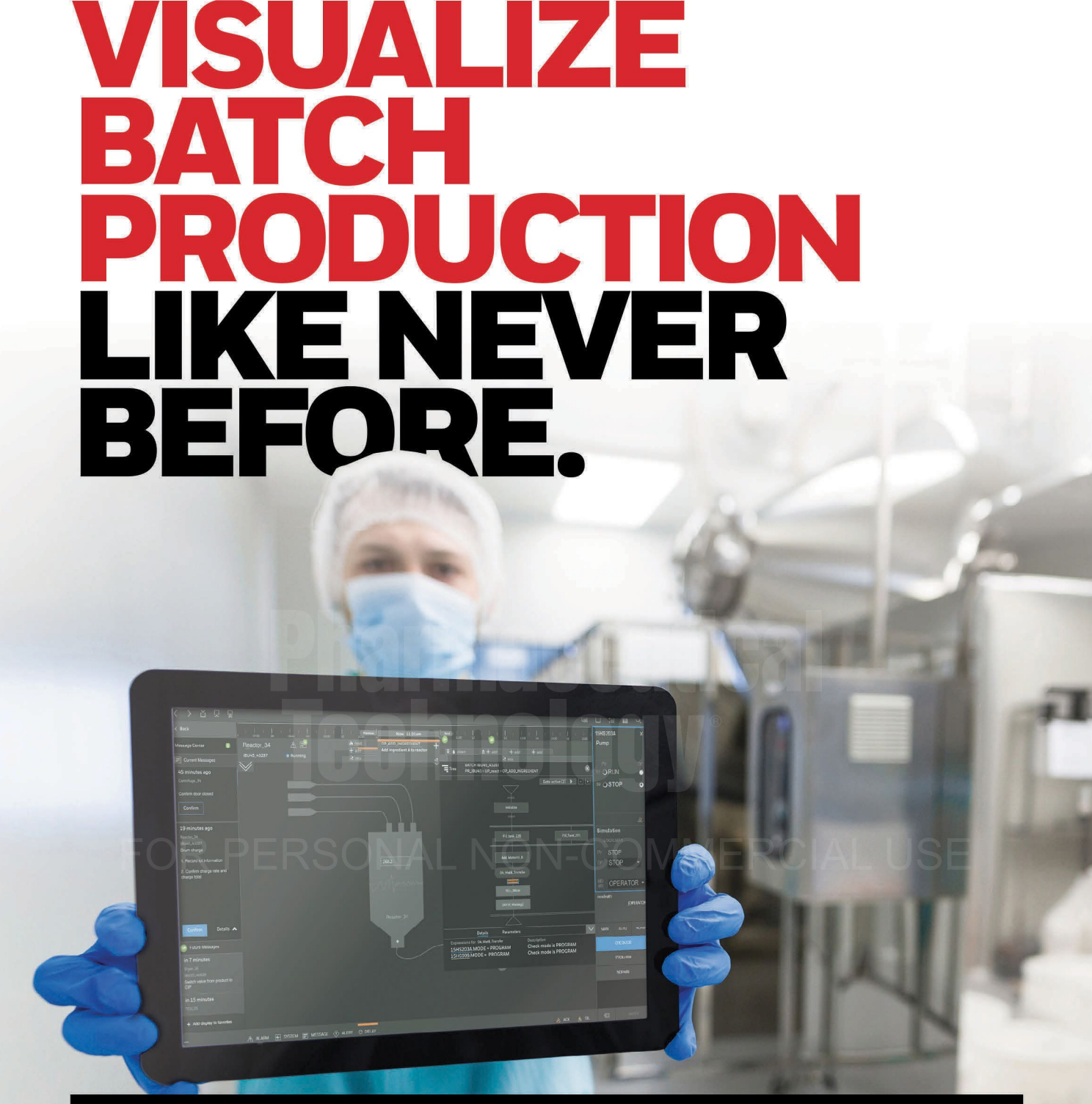

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Can Policy Keep Pace with Science and Discoveries?

Rita Peters

The promise of new therapies is tempered by the need for affordability, safety, and ethics.

Researchers continue to report exciting new discoveries in science and medicine that have the potential to improve life and address challenges facing society. The intersection of scientific opportunity and business profitability can, however, lead to ethical conflicts.

Emerging scientific methods such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) genome editing technology, which can be used to modify genes in living cells and organisms, offer the promise of correcting genetic mutations to treat genetic causes of disease. Researchers and ethicists generally agree that gene editing methods are suitable for research applications, but not for reproductive purposes.

Concerns about the misuse of gene-editing processes were realized when a scientist in China announced in November 2018 that he used CRISPR techniques to edit the genes in human embryos of twin girls with the intention of protecting them against the human immunodeficiency virus. This controversial work was denounced by scientists worldwide; in December 2019, a court in China sentenced the scientist to three years in prison for working outside the boundaries of scientific and medical ethics.

This experiment illustrates the ethical, safety, and legal issues associated with promising new scientific discoveries, and many unanswered questions associated with their long-term use. FDA has pursued enforcement action against dozens of unapproved therapies and treatments based on emerging sciences. In announcing a permanent injunction against a Florida-based facility for selling adulterated and misbranded cellular products, FDA noted there are many offenders selling unproved stem-cell products, and "These actors are taking advantage of patients, many in vulnerable positions with chronic or terminal diseases, by leveraging the widespread belief in the eventual promise of these products, flouting the statutes and our regulations "(1).

Beyond rooting out fraudulent efforts, FDA and industry experts also recognize the challenges with developing emerging therapies. FDA noted that while stem cell products have potential to improve human health, "… that potential will never be fully realized if careful scientific work and thoughtful clinical investigation supporting the safety and efficacy of these products are not conducted."

More than 1000 gene- and cell-therapy and other regenerative products are currently in the US clinical trial pipeline, illustrating the need for innovative development, manufacturing, and supply chain procedures and practices to deliver these therapies to patients. In an article in *BioPharm International*, experts from bioprocessing equipment manufacturers and contract development and manufacturing organizations emphasized that standardized commercial manufacturing platforms and processes are needed to ensure that these therapies can be delivered in a safe, cost-effective manner (2).

Emerging therapies are expected to contribute to the growth in global sales of prescription drugs from an estimated $839 billion in 2019 to $1.18 trillion in 2024, a compound annual growth rate of 6.9%, according to Evaluate Pharma. For the top 100 products by sales, Evaluate Pharma analysts expect biotech product sales to overtake conventional product sales for the first time. In addition, biotech products are forecast to represent 32% of prescription drug sales by 2024, up from 28% in 2018 (3).

Expensive, emerging therapies are becoming a larger share of the prescription drug market; however, solutions to the affordability question continue to trail rapid advances in science, threatening the success of these products. "The advances in cutting edge science are, for now, outpacing the traditional pricing and reimbursement systems the industry has been built on," Evaluate Pharma reported. "This disconnect is leaving both patients and payers wondering how accessible these life-altering products will be."

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References

1. N. Sharpless and P. Marks, "Statement on Stem Cell Clinic Permanent Injunction and FDA's Ongoing Efforts to Protect Patients from Risks Of Unapproved Products," Press Release, *www.FDA.gov* (June 25, 2019).
2. R. Peters, "Faster, Better Bioprocessing in 2020," *BioPharm International*, 33 (1) 12-14.
3. Evaluate Pharma, *World View 2019, Outlook to 2024* (12th edition, June 2019). **PT**

Rita Peters is editorial director of *Pharmaceutical Technology*. Send your thoughts and story ideas to rpeters@mmhgroup.com.

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Regulation to be Shaped by Pricing and Production Issues

Jill Wechsler

Pressures on FDA will affect industry's success in bringing new therapies to market.

While biopharma companies can anticipate continued success in discovering new gene and cellular therapies and in devising innovative treatments for multiple serious conditions, a range of issues are poised to shape R&D and regulatory policies in early 2020. Politicians on all sides will continue to hammer drug prices, prompting industry to emphasize the importance of maintaining strong investment in R&D. FDA will remain embroiled in addressing a number of high-profile public health issues, as well as drug shortages and complex drug development initiatives.

With national elections looming in November 2020, and a host of Democrats seeking to regain the White House, health policy and pharmaceutical costs will remain leading issues for all candidates. The future of the Obama Administration's Affordable Care Act hangs in the balance, with the debate poised to shape federal and state drug coverage and reimbursement as part of initiatives to lower outlays for medicines. Industry will challenge legislation authorizing drug importing or international reference pricing as a threat to continued innovation, but the full ramifications of election-year politicking remain to be seen.

Jill Wechsler
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Important challenges await FDA's new commissioner, Stephen Hahn, most notably ongoing efforts to address the nation's devastating opioid epidemic and to halt teen vaping of e-cigarettes, which has been linked to dozens of deaths. There's pressure on the agency to clarify its rules for cannabidiol products, particularly dietary supplements promoting health benefits, and to address concerns about the rise in antibiotic resistance and lack of research on new treatments to combat infectious diseases. Delays in Congress approving the federal budget for the 2019 fiscal year will continue to create difficulties for the agency in assuring support for its many crucial food and drug programs.

There's pressure on the agency to clarify its rules...

In response to the public outcry over drug prices, FDA will continue to streamline and accelerate the approval of more generic drugs and biosimilars as alternatives to expensive brand therapies. However, most of the biosimilars approved so far have yet to reach the market due to complex patent issues as well as efforts by innovators to discourage acceptance of follow-on therapies by physicians and health plans. FDA will continue to oppose tactics to delay access to comparators needed to test generics and biosimilars, and some policy makers look to prevent brands from offering financial incentives to health plans and pharmacy benefit managers (PBMs) to favor their products. But the issues are complex and will present challenges in bringing biosimilars and generics to patients.

Innovation and quality

FDA has worked to establish standards to support the development of innovative, life-saving cellular and gene therapies, as seen in the approval of several breakthrough products and industry programs to develop dozens more. Patient advocates will continue to provide important voices for shaping risk-benefit equations for promising therapies, while manufacturers will invest more in modern operations able to produce quality cutting-edge products more reliably and efficiently. All parties will be watching closely to detect any safety problems or signs of limited effectiveness that could raise concerns about the long-term value of a new treatment.

The importance of reliable systems for producing safe and high-quality pharmaceuticals will remain in the spotlight as part of efforts to ensure access to needed medicines. Congressional leaders are concerned about continued shortages in a number of critical treatments, as well as increased reliance on drug ingredients imported from China, India, and other countries. FDA's Office of Regulatory Affairs (ORA) is looking to implement more fully its pharmaceutical inspectorate process, which features highly trained

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EMA Launches Inspection Pilot Program

On Dec. 17, 2019, the European Medicines Agency (EMA) announced it was launching a pilot program to increase the inspection of facilities that manufacture sterile pharmaceuticals with its international partners (1). The pilot program will last for at least two years. EMA has a similar collaboration for the inspection of API facilities.

The collaboration between EMA, EU national authorities (France and the United Kingdom), the US FDA, Australia's Therapeutic Goods Administration, Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency, and the World Health Organization will allow the various agencies to share information on good manufacturing practice (GMP) inspections of companies that manufacture sterile drugs and who are located outside the participating countries. The collaboration will also allow the countries to organize joint inspections for manufacturing sites of common interest.

Reference

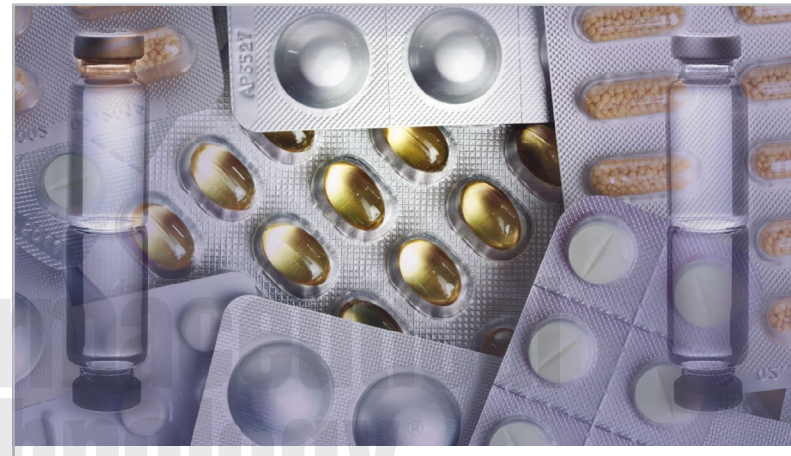
1. EMA, "Launch of International Pilot Programme on Inspection of Manufacturers of Sterile Medicines," Press Release, Dec. 17, 2019.

—*The Editors of* Pharmaceutical Technology

professionals using templates to evaluate how well production systems and practices can ensure the regular production of quality products, and to support industry efforts to modernize operations and address problems expeditiously.

More guidance from FDA should help improve testing and production of needed treatments, particularly new cellular and gene therapies that raise tricky quality control challenges. FDA will continue to support global harmonization of standards for drug production and for preclinical and clinical testing, as seen in a range of agreements with other regulatory authorities. These involve sharing and accepting reports on plant inspections, on certain testing programs, and more recently on information in market applications to achieve simultaneous drug approval decisions by multiple authorities. A main theme for the coming year will be to reduce extraneous requirements and promote more streamlined, risk-based approaches to drug development and production around the world.

Congress may do more to support these and other R&D programs by advancing legislation to further initiatives authorized by the 21st Century Cures Act five years ago. This time, the legislators indicate an interest in promoting wider utilization of digital health technologies to improve access to new products and health services; in modernizing coverage policies for innovative, life-saving drugs; and in utilizing real-world evidence more broadly in drug development. **PT**



Public Opinion: Can Pharma Chart a New Course?

Agnes Shanley

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As the high cost of drugs continues to erode public opinion, experts ask whether price controls are the best, or only, way to improve access to medicines and regain the public's trust.

Pharma has come a long way since the late 1980s, when Roy Vagelos, then CEO of Merck, promoted the image of an ethical and compassionate industry by making ivermectin, its treatment for river blindness, available to countries around the world at no cost. At the time, the late Sen. Edward Kennedy called the act "a triumph of the human spirit" (1).

Since then, as direct-to-consumer advertising took off in the United States, the industry's image began to change. Bolstered by media coverage of conflicts of interest in promoting products to physicians and first-hand accounts such as Jamie Reidy's book, *Hard Sell: Confessions of a Viagra Salesman* (2), the pharma sales representative began to eclipse the devoted researcher in public perception. As regulators and academics pointed out the need for pharma to control manufacturing costs (3), spending on manufacturing and quality were dwarfed by industry spending in other areas. The millennium's first decade saw criticism over pharma's expensive political lobbying and its clinical trial and patent extension practices, by physicians including Harvard Medical School professor Marcia Angell.

Negative publicity reached a high point in 2015, when former Turing Pharmaceuticals CEO Martin Shkreli increased prices for an anti-infective from $13.50 to $750 per pill (4); and in 2016, when Mylan first came under fire for cornering the market on EpiPen epinephrine (5) auto-injectors and increasing prices by more than 500% over a nine-year period; and Valeant Pharma executives were charged with fraud (6). That same year, the Project on Government Oversight questioned FDA's ties to the industry through the US Prescription Drug User Fee Act and its scientific independence in approving new rare disease therapies, and also drew attention to pharma's connection with patient advocacy groups (7).

Deteriorating public trust

Over the past 15 years, US public opinion polls have continued to reflect decreasing public trust in the industry, a trend that has been exacerbated by questions of corporate culpability in the opioid addiction crisis. In 2015, a Kaiser Health Tracking poll found that 72% of US citizens saw drug costs as unreasonable, with 70% believing that drug companies put profits before patients' lives, and 25% saying they found it difficult to pay for treatments their physicians had prescribed (8).

In October of 2019, a year that saw outcry over pricing for insulin, continued shortages of crucial commodity drugs, and Congressional hearings on the topic of drug pricing, a Gallup poll

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found pharma to be the least-trusted industry in the US (9). In December 2019, an international group of researchers launched the Pathways to Independence project in the *British Medical Journal* to explore how evidence of a drug's therapeutic value might be gauged more scientifically, divorced from all commercial interests (10).

Demands for government action

As the public and special interest groups have demanded government action on pricing, a number of proposals would impose limits on pharmaceutical prices, or bring them in line with the prices that patients in other countries pay. Other suggestions have called for establishing an independent US government agency focused exclusively on pharmaceutical pricing (11).

While it is not certain that any of these proposals will be voted into law, some observers ask whether both sides of the pricing debate are missing the point. Exploring some of these issues is *The Great American Drug Deal: A New Prescription for Innovative and Affordable Medicines*, which will hit bookstore shelves on January 20, 2020 (12). Author Peter Kolchinsky is a doctorate-level scientist and founding partner of RA Capital Management, a Boston-based investment fund that focuses on forming and funding biotech companies that are developing new medicines, medical devices, and diagnostics. He shared insights with *Pharmaceutical Technology*.

Distinguishing between innovation and patent extension

Kolchinsky says he wrote *The Great American Drug Deal* in response to misunderstandings about drug pricing and innovation costs. "Companies that we are working with and funding to develop new drugs never intended for those drugs to be unaffordable to anyone. They want patients to benefit from their inventions," he says. But these small innovators would be hurt by sweeping price controls, he says.

One problem is that, when the public and Congress look at the drug industry, they see a single, abusive business model when there are really two distinct models, Kolchinsky says. One model drives innovation and needs to be preserved, while the other takes advantage of society and must be reformed. In the first, companies develop new drugs with the hope of marketing them for a period of 10–15 years before they go generic. In the second, they extend the lives of older drugs with new patents, often by making minor upgrades, some of which do not add much value, or simply by exploiting regulatory loopholes so that they can keep harvesting branded revenues. Efforts to reform the industry should largely be focused on the second model, Kolchinsky says, and aim to prevent unjustified patent extensions rather than to impose direct price controls on all drugs.

Pharma's social contract

Kolchinsky uses the concept of the "biotech social contract" to explain what should be expected from innovators, the industry, and society. Public policy should reward innovators for the period during which their drug is patented, after which, Kolchinsky says, a process called "contractual genericization" should be used to prevent companies from engaging in frivolous patent extensions.

Under contractual genericization, all drug companies would have to enter into a contract with a dedicated government agency at the time they file for approval of a new drug. They would not be able to get approval without signing that contract, which would ensure that the drug becomes inexpensive once the initial patent period has expired, Kolchinsky explains. "If a company were to make a legitimate, useful but straightforward upgrade to the drug after it launches, it could then apply for and receive a deferral of the contractual genericization date, permitting six more months of branded revenues, analogous to the way that FDA awards six months' additional patent exclusivity in exchange for running pediatric trials," he says. In addition to bringing about contractual genericization, Kolchinsky believes that legislation should focus on insurance reform and ensuring that patients' out-of-pocket costs are minimized or even eliminated. "Insurance companies have increasingly been shifting costs on to patients, which has intensified public outrage," he says.

The international price index

One form of price control that is currently being discussed is use of an International Price Index (IPI), requiring that companies set US prices to be comparable to those they charge in European countries. Marc Rodwin, professor of law at Suffolk University in Boston, who has studied the way that European markets measure cost effectiveness and set prices, sees this approach as having potential benefits. Rodwin's research has focused on practices in France (13), where the government sets a maximum price based on comparing the value of a new drug to that of its closest equivalent treatment. If a company doesn't like the price, it can walk away, although that rarely occurs, Rodwin says.

In order for international price benchmarking to work, however, the US would have to consider off-list discounts, Rodwin says. Kolchinsky believes that syncing US drug costs to either list or net prices in other countries would lead to higher prices. "If drug companies have to charge the same for a drug in US and Europe, they will simply export the US price to Europe. In some cases, Europe will refuse to pay, denying patients treatment. With less revenue and profits from Europe, companies would be forced to make up the difference by charging the US more, thus raising the global price and further reducing Europe's participation," he says, noting that this view was corroborated by the US Congressional Budget Office's own analysis (14).

Drug pricing agency

Kolchinsky's big idea in *The Great American Drug Deal* is the introduction of the concept of contractual ge-

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nericization to ensure that all drugs go generic without undue delay.

But Rodwin counters, "Ending abusive patent extensions will only touch at the margins [of the pricing problem]. The key question is: Must purchasers pay any price that a drug developer says that it wants?"

Taking NICE's approach

Rodwin believes that the idea of a separate government agency focused on pricing could work in the US, but he wants to see it negotiate for launch prices, an approach that Kolchinsky insists would be toxic to innovation. Rodwin says, "The UK developed the National Institute for Health and Care Excellence (NICE) over time, and the US could develop its own approach. It already has a physician payment assessment commission for Medicare."

"If I were advising US legislators, I'd say they need to first establish the principle that they have the ability not to purchase a drug if it's not worth it, and to use existing resources to establish value. If the federal government established that principle for its own purchasing in the Veterans Administration, Department of Defense, Medicare and Medicaid, the private sector might choose to piggyback on that," Rodwin says.

"If Medicare were to develop a thoughtful way to assess a pharmaceutical's value like the approach that is used by NICE, or if it developed a system that incorporated the approach used in France (i.e., one that considers the added value of a new drug), large private insurance companies might choose to use this methodology, and we wouldn't have to change US systems in one fell swoop," Rodwin says.

Even on a limited basis, he says, adopting these approaches could work. "If we could incorporate some of these changes, just for Medicaid and Medicare, which account for nearly half of the market, it would have a substantial impact on government spending and on individual copayments," he says.

The danger of losing R&D incentives

Kolchinsky argues forcefully against attempts to control launch prices or deny patients access to innovative therapies. "The cuts we can make are in what we spend on old drugs, but we mustn't cut the incentives for new ones or the response will be a predictable and swift reduction in funding of work to treat any disease that the price-setting government agency appears to undervalue," he says. As an example of what might go wrong, Kolchinsky points to the dearth of industry investment in antibiotics (15), which has prompted a call for establishing incentives for discovery and development.

Using the BARDA model

If an independent pricing agency is established in the US, Kolchinsky thinks it should be structured, not like NICE but like the US Biomedical Advanced Research and Development Authority, which stockpiles biodefense vaccines and guarantees that developers and manufacturers make a specific profit for their highly specialized products. "Such an agency could hold the generication contract on every drug, guaranteeing that its price would drop to, say, twice the cost of production after initial patents expire. It could modestly extend that date to reward a useful upgrade of the drug after it is launched (e.g., moving from a twice-daily to a daily dose)," says Kolchinsky.

There would still be room for drugs to go generic the conventional way, he explains, through competition amongst several generic versions, but if the price didn't drop low enough due to competition, the contract would serve as a back-stop and the original manufacturer would either have to provide it at the guaranteed low price or else transfer the contract to another company that would honor it.

"If multiple companies were interested in the contract, they could bid for it. But at all times someone would be accountable for making the drug and selling it at a modest, yet still profitable price. As a last resort, if a nonprofit company wanted to manufacture the drug, the government could contract with it to make the drugs that nobody wants to make, many of which are in short supply," Kolchinsky explains.

Clearly, the debate over high US drug prices promises to continue. But perhaps, as Kolchinsky suggests, it's time for all stakeholders —industry, insurers, and the government —to consider obligations, not only to the present generation but to future generations of patients, and to redefine the social contract and the roles they each should play in it.

References

1. *New York Times* Editors, "Merck Offers Free Distribution of New River Blindness Drug," *nytimes.com*, Oct. 22, 1987.
2. J. Reidy, *Confessions of a Viagra Salesman*, (Andrew McNeel Publishing Co., Kansas City, MO, 2005).
3. S. Neuman, "The Pharmaceutical Industry Wastes $50 Billion a Year Due to Inefficient Manufacturing," *wustl.edu*, Oct. 9, 2006.
4. A. Mohdin, "A Drug Firm Defends Raising the Price of a Life-Saving HIV Drug by a Mere 5,000%," *qz.com*, Sept. 22, 2015.
5. E. Willingham, "Why Did Mylan Raise the Price of the Epi Pen by 400%? Because It Could," *forbes.com*, August 21, 2016.
6. M.Egan, "Valeant Executives Arrested for Fraud," *cnn.com*, Nov. 17, 2016.
7. D. Hilzenrath, "FDA Depends on Industry Funding; Money Comes with Strings Attached," *pogo.org*, Dec. 1, 2016.
8. Di Julio et al., Kaiser Health Tracking Poll, *kff.org*, Aug. 11, 2015.
9. J. McCarthy, "Big Pharma Sinks to the Bottom of Industry Rankings," *gallup.com*, September 2019.
10. R. Moynihan et al., "Pathways to Independence," *bmj.com*, Dec. 3, 2019.
11. US Dept. of Health and Human Services, "HHS Advances Payment Model to Lower Drug Costs for Patients," Press Release, *hhs.gov*, Oct. 25, 2018,
12. P. Kolchinsky, *The Great American Drug Deal*, Evelexa Press, Boston, 2020.
13. M. Rodwin, "What Can the United States Learn from Pharmaceutical Spending Controls in France?" *Commonwealth Fund Report*, Nov. 11, 2019.
14. P. Swegel, "Effects of Drug Price Negotiations, a Letter to Senator Frank Pallone," *cbo.gov*, Oct., 11, 2019.
15. V. Simplin et al, *J. Antibiotics* 70(12), 2017, pp 1087-1096. **PT**

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Human-Centered Work: How Pharma Can Move to a Blame-Free Culture

Agnes Shanley

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As mergers continue and operations become more complex, simplifying procedures and training can prevent costly morale, quality, and compliance problems.

When something goes wrong at a facility, the first and easiest explanation is often operator error. But experts say that is rarely the real reason. Today, a growing number of FDA warning letters (see feature, p. 60) find that some facilities are not maintaining or following written procedures, whether for process or equipment operation, validation, or quality control testing.

Experts trace this problem to a need for more human-centered documentation and training practices, and approaches that empower staff and encourage their active involvement in problem solving and improvement. "Anywhere there is a person-machine interface, there is an opportunity for error" says Jim Morris, executive director of the Health Sciences division of NSF International, a global consulting group that focuses on training, testing, and auditing for pharmaceutical and medical device companies. "The information that operators have about how a process works becomes all the more important," he says. The more that such information can be provided succinctly and clearly, the greater the chances that procedures will be carried out correctly.

Generally, operations that involve bioprocessing equipment come with a high level of complexity, says Morris. However, the highest bar for operators is in sterile operations, he says, due to the nature of the operations and the risk of microbiological contamination. Equipment vendors have responded by developing isolators and enclosed systems that minimize operator contact with the product.

Use of lean manufacturing and operational excellence techniques has also shown results by reducing waste and errors, and boosting overall productivity. Vetter, a contract development and manufacturing organization, recently implemented such a system for its aseptic filling operations, and realized an overall improvement in production flexibility and efficiency (1).

Complex changeovers

Outside of biopharma, changeovers for continuous oral solid dosage (OSD) form processing are extremely complex, says Morris, often involving more than 1000 components to disassemble, clean, and reassemble. Ideally, changeovers should take a day or two, but for continuous OSD facilities, they can require a week or more, depending on the complexity involved (2). Equipment vendors are working on simplifying designs, in projects that involve industry and academia, but work remains to be done.

Operators are the best source of insights on how to improve documentation and processes, and proactive companies are setting up processes that get the operators and technicians who are actually doing the work to provide feedback on procedures and training to see how they might be improved.

Seeking input from staff requires creating an open culture in which individuals feel safe bringing up problems and highlighting practices and areas that may need to be improved. "There is a need to move from blame and fear, and to shift the emphasis from a reactive to a proactive culture that provides a nurturing environment [for employees]," says Nuala Calnan, principal of the consulting firm BioPharm Excel, professor at the Technical University of Dublin, and co-leader of the International Society for Pharmaceutical Engineers' (ISPE's) and PDA's quality culture program.

But even voicing the idea of employee empowerment can be challeng-

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ing in a business environment that is constantly changing and focused on reducing costs. In 2019, the pharmaceutical industry saw $278 billion in mergers and acquisitions, 12% of the world's total, according to Bloomberg analysts (3). Each change in company ownership brings changes in priorities, focus, systems, and procedures.

"Where you have a lot of structural and management changes and pressure on costs, change filters its way down to how work is conducted. It's difficult to work with a lot of continuity, and people will be more prone to error," says Morris. "The key to improving performance is to set up systems and people for success. Reducing complexity through user-focused documentation systems and risk-based quality systems are key components of success," he says.

Risk-based triage

NSF advances an approach, discussed in a 2019 webcast (4), that is based on triage, or prioritizing efforts based on the severity of potential risks of failure. "Not all events are created equal," Morris said on the program, "but many sites don't triage very well, as attested to by poor investigations, a large number of open root cause investigations, and open CAPAs, recurring compliance issues, and high levels of stress."

Successful triage requires establishing clear risk thresholds to distinguish between low-, medium-, and high-level risks and treating them so that staff effort devoted to an event or investigation is a function of the level of risk involved, he said. Training should also be designed so that crucial tasks (particularly the fundamentals of current good manufacturing practices [CGMPs] such as gowning, batch recordkeeping, and data logging) are practiced often and become embedded as habits.

At the same time, standard operating procedures (SOPs) should be made easier for operators and technicians to understand and follow, Morris said. Many pharma and biopharma SOPs still contain unnecessary or redundant information or appear as straight text, which can make them difficult to refer to quickly in a busy work environment where individuals are multi-tasking and frequently interrupted, Morris said on the program.

User-friendly SOPs

It is also important to address the user-friendliness of SOPs, which are meant, not to satisfy regulators or to function as training aids, but to standardize processes and provide consistency, as Martin Lush, global vice-president for pharma and biotech at NSF International has pointed out (5). At a typical pharmaceutical facility, Morris said on the webcast, there may be 800 SOPs and 200 work instructions in place, where the ideal situation might be to have the reverse (i.e., 200 SOPs and 800 work instructions).

In addition, each individual SOP can exceed 50 or 75 pages and can be very difficult to follow, Morris said. He suggested using smart labels, for example, to convert a full page of text into a label that provides built-in instructions, and to use arrows and flowcharts to describe sequential tasks, adding photos and call outs to improve explanations."We need to make sure that SOPs are well designed so that the information they present is relevant and written so that people can follow it, and this needs to be an area of focus for most, if not all, pharmaceutical companies today," he says.

Morris sees a potential role for virtual and augmented reality, especially in setting up risk-free learning environments, so workers can get close to the environment without posing any contamination or other risk. Embedded video will be especially useful in optimizing SOPs for complex and unique operations, says Morris.

He blames inadequate planning for many operations and compliance problems. "In some cases, companies haven't invested enough in understanding variability, and how a process will perform at scale in their operations. Some don't spend enough time ensuring that people are prepared for the new way of working before they bring changes online. As a result, they suffer from nonconformances that need to be investigated," he says.

Empowering those employees closest to problems to solve them is a win-win, freeing managers up for more strategic work, says Calnan. "All too often in a CGMP facility, individuals must operate almost as if they are in a straightjacket within the restrictions of SOPs, regulations, and processes that are in place," she says.

In these situations, the leader may handle all the directing and make all the decisions, says Calnan. "We need to enable qualified workers to make as many of those decisions as close to the call space as possible with all the support that they need," she says.

Incentivizing problem-solving

Calnan also advises setting up polices that reward people for preventing or predicting problems. One example, would be rewarding good catches (e.g., discovering whether any crucial documentation is missing before product release) as part of batch documentation. In the end, senior management support is essential for shifting from a reactive to a proactive culture and empowering employees. "Quality culture comes from leaders, and you won't get that crowdsourcing of problem solving and proactivity from the ground floor up if it isn't sponsored from the top down," she says.

References

1. G. Buerkle, "Applying Operational Excellence to Improve Injectable Production," *PharmTech.com*, June 24, 2019.
2. J. Markarian, "Oral Solid Dosage Continuous Manufacturing Strategies," *PharmTech.com*, April 2, 2019.
3. G.M. Burnett, "Analysis: Pharmaceutical M&A Accounted for 12% of all Global Deals in the Third Quarter of 2019," *bloomberglaw.com*, October 15, 2019.
4. J. Morris, "Implementing a Simplification Strategy," *youtube.com*, April 10, 2019.
5. M. Lush, "SOP Simplification, Part 1," *youtube.com*, May 31, 2017. **PT**

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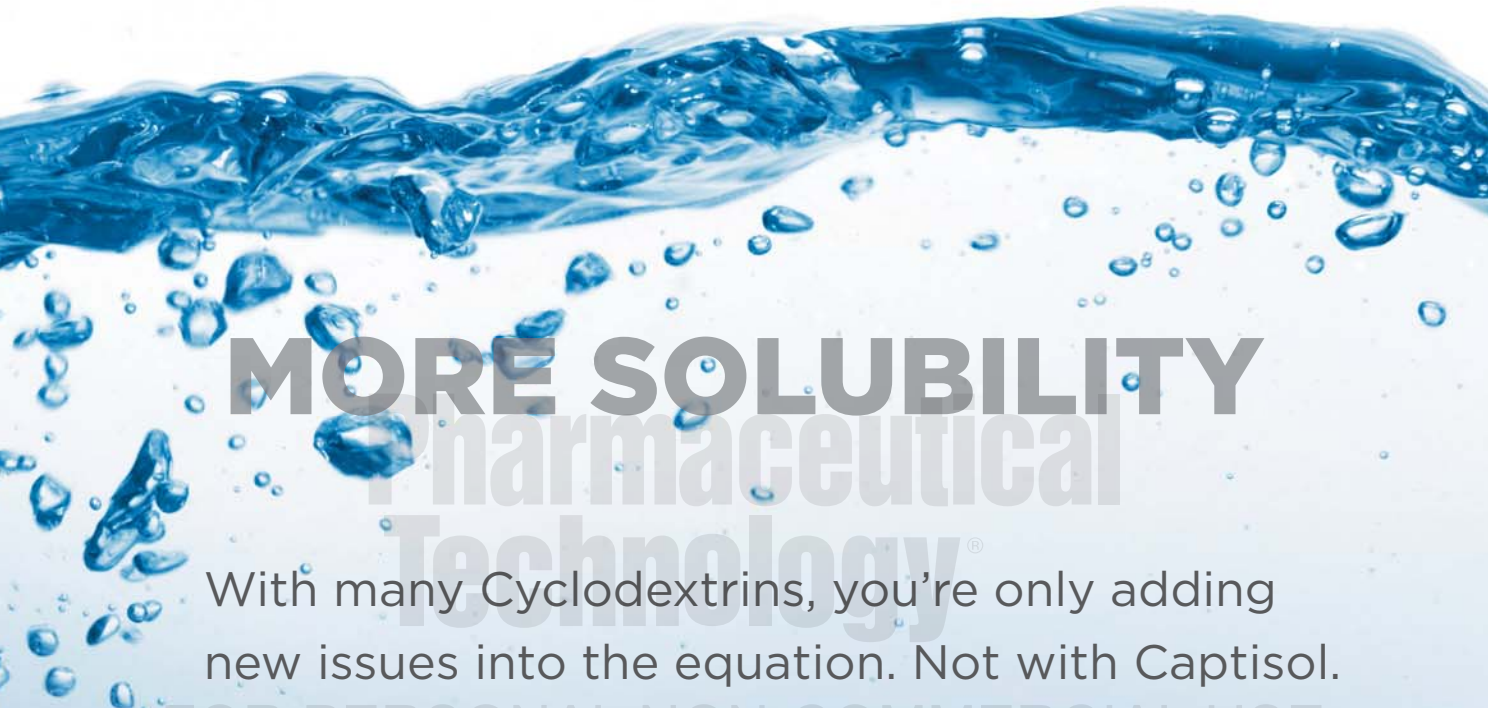

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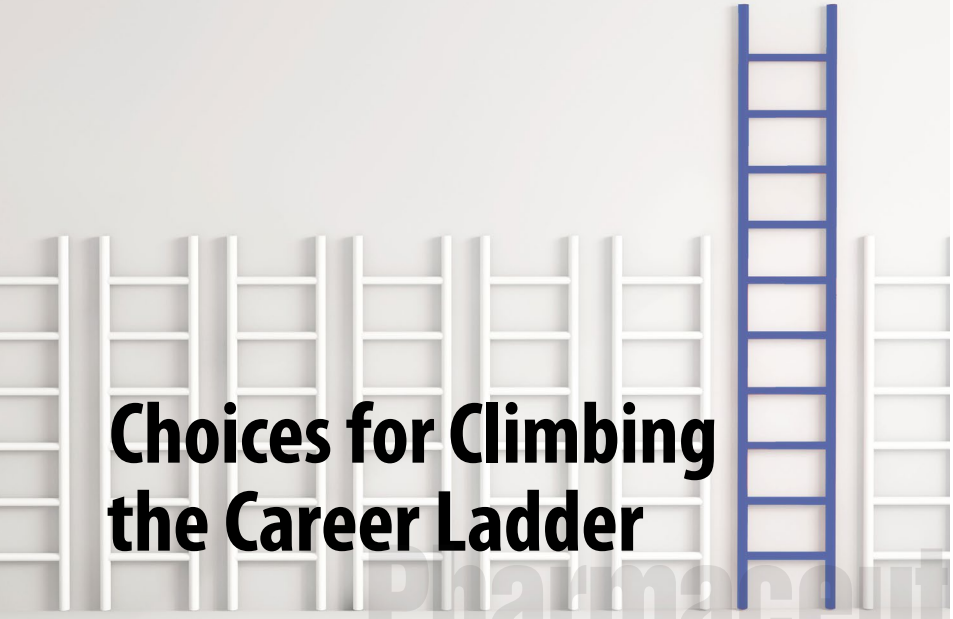

Choices for Climbing the Career Ladder

Rita Peters

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With a positive employment market, some bio/pharma professionals explore options for career advancement.

An employee's view of the job market is often colored by recent work experiences—whether positive or negative—and their most recent salary increase. Professionals working in biopharma drug development and manufacturing are concerned about the size of their paychecks, but other factors—including challenging work, job security, and company stability—may be more important when making career change decisions.

Insight provided by bio/pharma professionals from around the world responding to *Pharmaceutical Technology*'s annual employment survey (1) indicates strong confidence in the biopharma industry (66% expect business improvement in 2020) and some confidence in prospects for their employer (52% expect business improvement in 2020). More than half of the respondents, however, expressed interest in seeking better opportunities beyond their current position. (See the infographics on pages 26–27 for an overview of survey results.)

Job insecurity, company restructuring, a lack of training, an unsatisfactory work/life balance, and uncertainty about the company's performance or success were the top reasons for job dissatisfaction.

Similar to previous surveys (2–3), more than half of all respondents said they would like to leave their jobs, given the opportunity; however, 58% said they do not expect to leave in the coming year. A significant segment, 19%, said they would like to change careers and leave the bio/pharma industry.

Prime time for a job change?

Survey results indicate bio/pharma professionals are on the move. More than 44% of 2019 respondents—compared with one-third in 2018—said they stayed with the same employer, on average, for five or fewer years. Respondents working in large-molecule drug development and manufacturing stayed with the same employer longer than those in the small-molecule market segment.

More than one-quarter of the respondents said they voluntarily changed jobs in the past two years. The reasons cited—with multiple choices allowed—were to pursue a better career opportunity (72.7%), find more challenging work (40%), or to seek a better work-life balance (32.7%). Those working in the biologic drug segment valued company stability more than their counterparts in the small-molecule segment, who said job security was more important.

Salary was the fifth most-cited single reason for job change, trailing work/life balance, professional advancement, intellectual challenge, and job security. Nearly two-thirds of the respondents were confident they could find a job similar to their current position, should they choose—or were forced—to find new employment.

In the past two years, nearly one-quarter of the respondents said their company experienced a merger or acquisition, up from 18.1% in the previous survey; an additional one-quarter of the respondents reported that their companies had been through a downsizing or restructuring. Nearly 20% of the respondents said they left the company due to such an acquisition, downsizing, or restructuring.

Respondents suggest there is a positive market for job seekers; 36.8% of respondents said there are few qualified candidates for open scientific/technical positions (almost 40% for biologics positions), compared with 30.3% in 2018. A smaller percentage (28% in 2019 vs. 34.2% in 2018) said there were more qualified candidates than open positions. As in previous surveys, respondents expressed somewhat negative opinions about the knowledge and skill sets of new hires; 73% said the new hires were adequately trained but not exceptional; 18% said they were poorly trained.

Article contin. on page 66

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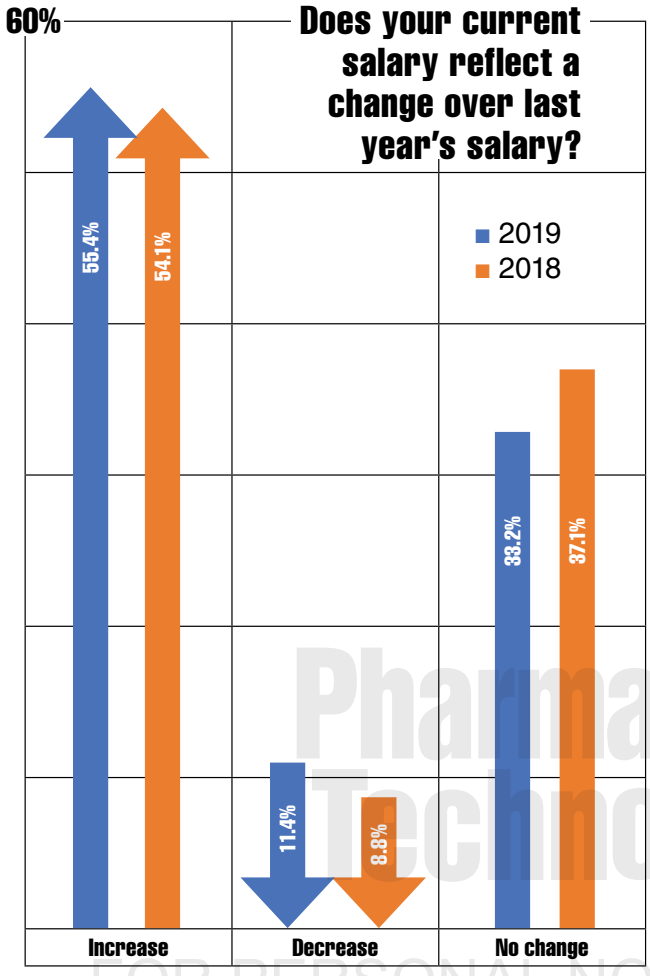

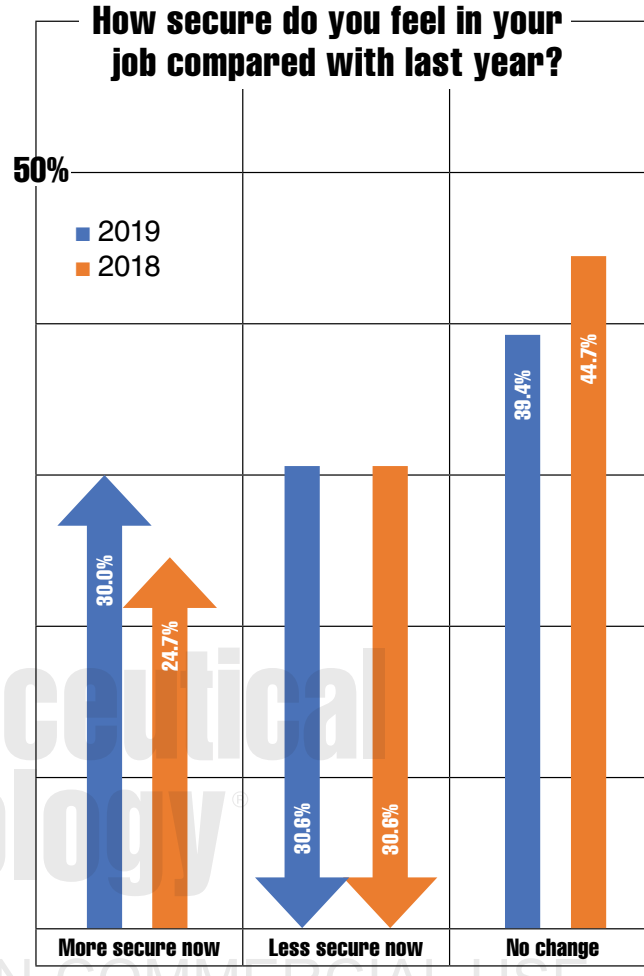

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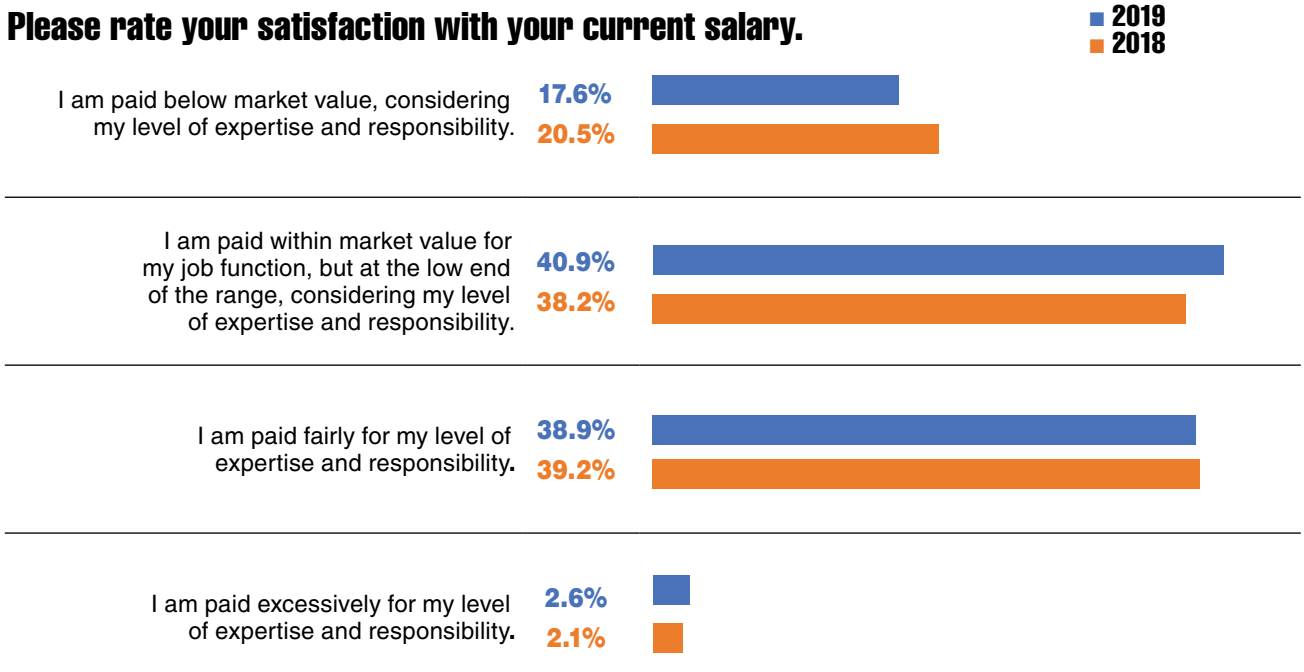
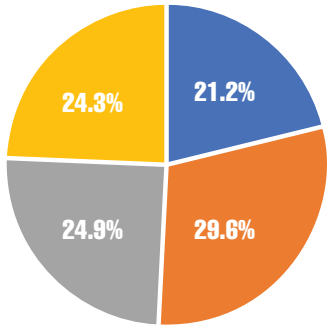
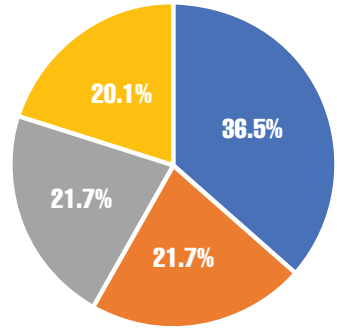


GRAPHICS BY MARIA REYES.

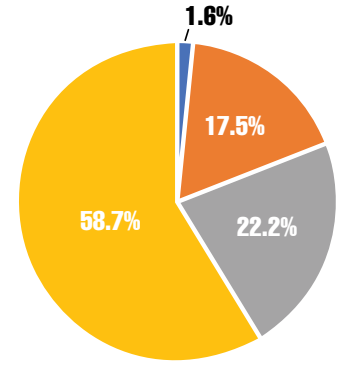
Bio/pharma workers contemplate job and career changes.



I would like to leave my job, given the opportunity.



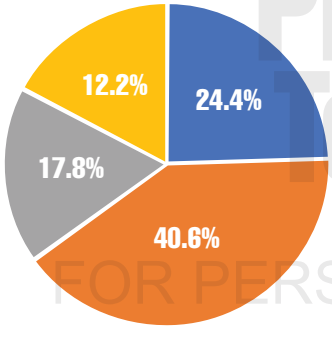
I do not expect to leave my job in the coming year.



I would like to change careers and leave the bio/pharma industry.

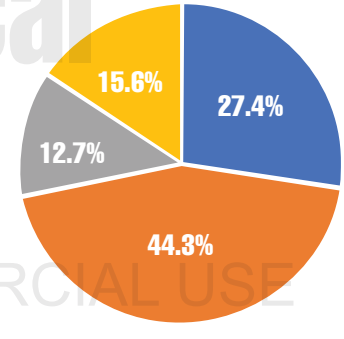
If it were necessary for you to change jobs this year, how would you assess the job market?

2019



- It would be straightforward to find a job comparable to the one I have now.
- It would take a while, but I would be able to find a job comparable to the one I have now.
- It would be straightforward to find a job, but it probably wouldn't be as good as the one I have now.
- I would have to search hard and be prepared to take what I could get.

2018



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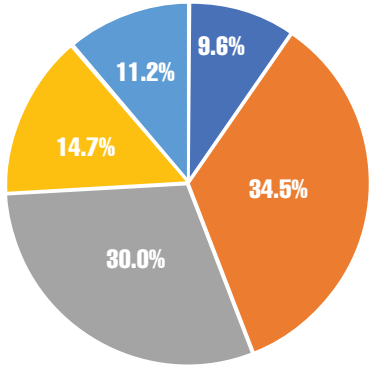
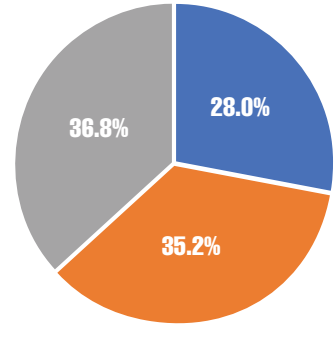
In your career, how long, on average, have you stayed with the same employer?



- Less than 2 years
- 3 to 5 years
- 6 to 10 years
- 11 to 20 years
- More than 20 years

Which statement best describes the job market for scientific or technical positions in bio/pharmaceutical development and manufacturing in your geographic area?



- Competition for open positions is strong.
- Competition for open positions is moderate.
- Employers compete for qualified candidates.

DUE TO ROUNDING, SOME PERCENTAGES MAY NOT ADD UP TO 100%. RESULTS BASED ON 2019 *PHARMACEUTICAL TECHNOLOGY/BIOPHARM INTERNATIONAL* EMPLOYMENT SURVEY.

US Maintains Lead in Drug Development Despite Fewer Approvals in 2019

Cynthia A. Challener

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FDA's approval rate slowed, but the US agency is still ahead of its international counterparts in green-lighting new drugs for market.

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The FDA continues to approve drugs at a rapid pace, although fewer novel drugs (48) were approved by the Center for Drug Evaluation and Research in 2019 (1) compared with 59 in 2018 (2). Compared with other agencies around the world, however, FDA again lead other leading regulatory authorities in the number of approvals.

According to the Kyoto Encyclopedia of Genes and Genomes Drug Database, 35 drugs with new active ingredients were approved in Japan by the Pharmaceutical and Medical Devices Agency (PMDA) as of Nov. 4, 2019 (3), while the total number of European public assessment reports (EPAR) authorized medicines as of Nov. 1, 2019 that were novel included 15 based on new molecular entities, approved under a biologic license application, and one cell therapy (4). In India, just 16 new drugs were approved by the Central Drugs Standard Control Organization as of mid-November (5).

Looking at specific drugs, only one—Skyrizi (risankizumab-rzaa) from AbbVie for treatment of psoriasis—was approved in the United States, Europe, and Japan; the therapy was approved in Japan approximately one month in advance of approval in the US and Europe. Rozlytrek (entrectinib) and Evenity (romosozumab-aqqg) were approved in both the US and Japan, with the latter receiving approvals just days a part, and the former getting the okay in Japan two months before it received approval in the US (6).

Interestingly, many more drugs in 2018 were approved in two or all three jurisdictions, and several of the drugs approved in the US and Europe in 2018 didn't receive approval in Japan until 2019, including Erleada (apalutamide), more than one year later, Braftovi (encorafenib), three to six months later, Mektovi (binimetinib), three to six months later, and Onpattro (patisiran sodium), 10 months later.

Many other drugs approved by FDA in 2018 did not receive approval by the European Medicines Agency (EMA) and/or PMDA until 2019, including Crysvita (burosumab), Trogarzo (ibalizumab), Palynziq (pegvaliase), Epidiolex (cannabidiol), Ajovy (fremanezumab), Lorbrena (lorlatinib), Vizimpro (dacomitinib), Libtayo (cemiplimab), Talzenna (talazoparib tosylate), Vitrakvi (larotrectinib sulfate), and Ultomiris (ravulizumab).

A study of decisions by FDA and EMA for 107 new drug applications during the period 2014–2016 found that the two agencies were in agreement on the majority (more than 90%) of approval decisions (7). Differences were largely due to different conclusions regarding efficacy, sometimes based on the same data and sometimes on differing data.

In a separate study, it was found that FDA approved 170 new therapeutic agents between 2011 and 2015, while EMA granted marketing authorization to 144 (8). In addition, the median total review time at FDA was much lower, on average 60 days shorter. FDA also approved more orphan drugs than EMA (43.5% vs. 25.0% of the total).

FDA approves many "firsts" in 2019

Many of the new therapies approved by FDA in 2019 were developed to treat rare diseases, and most of these drugs are the first treatments ever approved for these diseases. Examples include Celgene's Reblozyl (luspatercept–aamt), which reduces the need for blood transfusions in anemic patients with beta thalassemia (9); Ablynx's Cablivi (caplacizumab-yhdp) injection, the first therapy specifically indicated, in combination with plasma exchange and immunosuppressive therapy, for the treatment of adult patients with acquired thrombotic

Cynthia A. Challener, PhD, is a contributing editor to *Pharmaceutical Technology*.

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Study demonstrates digitalization of tablets for product authentication

A supply-chain simulation has demonstrated a secure, direct link between a physical tablet (placebo) and a digital backend, without having to rely on the traditional approach of authenticating traditional packaging barcodes.

The demonstration—conducted by PwC Australia, Colorcon, and TruTag Technologies—tested the mass digitalization of pharmaceutical tablets and their linkage to a Trillian-based trust ledger, demonstrating a step toward ensuring supply-chain integrity and addressing the problem of patient non-adherence, the companies reported in a Dec. 10, 2019 press statement.

The solution features three components: a Colorcon coating system infused with spectrally-encoded particles—or TruTags—that act as edible barcodes, a cell phone-based authentication application to decode and verify the embedded TruTags and link the physical tablet to the third component, a Trillian-based distributed ledger operated by PwC Australia.

"This technology represents a new era of security and transparency for the pharmaceutical industry in which patients can be empowered to authenticate their own medicines," said said Kelly Boyer, general manager, film coatings of Colorcon, in the press statement.

Reference

1. Colorcon, "Technology Coalition Prove Out the Mass Digitalization of Pharma Pills," Press Release, Dec. 10, 2019.

—*The editors of* Pharmaceutical Technology

thrombocytopenic purpura, a rare and life-threatening blood clotting disorder (10); and Pfizer subsidiary FoldRx's oral therapies Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis), the first FDA-approved treatments for heart disease caused by transthyretin mediated amyloidosis (11).

Other therapies for rare diseases for which the first new drugs were approved by FDA in 2019 include Givlaari (givosiran) from Alnylam Pharmaceuticals for acute hepatic porphyria, a genetic disorder resulting in the buildup of toxic porphyrin molecules (12); Turalio (pexidartinib) from Daiichi Sankyo for symptomatic tenosynovial giant cell tumor, a non-malignant tumor that causes the synovium and tendon sheaths to thicken and overgrow (13); targeted therapy Adakveo (crizanlizumab-tmca) from Novartis for vaso-occlusive crisis, a common and painful complication of sickle cell disease (14); and Scenesse (afamelanotide) from Clinuvel for pain due to phototoxic reactions upon exposure to light (15).

Several of the approved drugs are designed to treat cancer, including the first PIK3 inhibitor Piqray (alpelisib) from Novartis (16). The drug is used in combination with the FDA-approved endocrine therapy fulvestrant, to treat postmenopausal women, and men, with hormone receptor-positive, human epidermal growth factor receptor 2-negative, PIK3CA-mutated, advanced or metastatic breast cancer. The disease must be detected with companion diagnostic test therascreen PIK3CA RGQ PCR Kit from QIAGEN Manchester, which also received FDA approval in 2019.

Of note, Piqray was the first new drug application for a new molecular entity approved under the Real-Time Oncology (RTOR) pilot program, which permits FDA to begin analyzing key efficacy and safety datasets prior to the official submission of an application, allowing the review team to begin their review and communicate with the applicant earlier. Piqray also used the updated Assessment Aid, a multidisciplinary review template intended to focus FDA's written review on critical thinking and consistency and reduce time spent on administrative tasks. With these two pilot programs, Piqray was approved approximately three months ahead of the PDUFA VI deadline.

Two of the new drugs approved by FDA in 2019 address medical conditions suffered by women. Zulresso (brexanolone) injection from Sage Therapeutics is the first drug approved by FDA specifically to treat postpartum depression (17). Vyleesi (bremelanotide) from AMAG Pharmaceuticals treats acquired, generalized hypoactive sexual desire disorder in premenopausal women (18). FDA identified female sexual dysfunction as one of 20 disease areas of high priority and focused attention in 2012.

Alternative delivery methods

Some of the drugs approved by FDA are interesting due to their route of delivery. Novo Nordisk's Rybelsus (semaglutide), oral tablets, is the first glucagon-like peptide receptor protein approved by the agency to improve control of blood sugar in adult patients with type 2 diabetes that does not need to be injected (19). Baqsimi nasal powder, from Eli Lilly and Company, meanwhile, is the first glucagon therapy approved by FDA for the emergency treatment of severe hypoglycemia that can be administered without an injection (20).

Also of note was the agency's approval of Janssen Pharmaceuticals' Spravato (esketamine) nasal spray, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (21). Esketamine is the s-enantiomer of ketamine, which was approved under the brand name Ketalar in 1970.

New antibacterial, antiviral and antifungal meds

Developing new antibiotics and antiviral agents is a priority of FDA as concerns over drug resistance continue to rise; three 2019 approvals fall under this category. The Global Alliance for TB Drug Development received approval for Pretomanid tablets in combination with bedaquiline and linezolid for the treatment of a specific type of highly treatment-resistant tuberculosis (TB) of the lungs (22). This drug was approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs pathway and also received FDA's Qualified Infectious Disease Product (QIDP) designation and a Tropical Disease Priority Review Voucher.

Nabriva Therapeutics' Xenleta (lefamulin) was approved for the treatment

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of with community-acquired bacterial pneumonia and also received QIDP designation (23). Fetroja (cefiderocol), an antibacterial drug from Shionogi & Co. for treatment of complicated urinary tract infections also received the QIDP designation (24).

FDA also approved Sentosa SQ HIV Genotyping Assay (Vela Diagnostics USA), the first HIV drug resistance assay that uses next-generation sequencing (NGS) technology (25).

New pediatric therapies

One of FDA's 2019 approvals making significant news for its price and questions about data integrity was for Zolgensma (onasemnogene abeparvovecxioi), the first gene therapy approved to treat children less than two years of age with spinal muscular atrophy (SMA), the most severe form of SMA and a leading genetic cause of infant mortality (26). AveXis, which is a division of Novartis, also received a rare pediatric disease priority review voucher.

The oral drug Ruzurgi (amifampridine) from Jacobus Pharmaceutical Company was granted the first FDA approval of a treatment specifically for pediatric patients with Lambert-Eaton myasthenic syndrome (27). Pfizer's Fragmin (dalteparin sodium) injection, initially approved for adults in 1994, received approval for reducing the recurrence of symptomatic venous thromboembolism in pediatric patients (28).

AbbVie's oral drug Mavyret (glecaprevir and pibrentasvir), approved to treat hepatitis C virus (HCV) in adults in 2017, received approval for the treatment of children in 2019 (29). GlaxoSmithKline also won approval for Benlysta (belimumab) intravenous (IV) infusion (initially approved for adults in 2011) for treatment of children with systemic lupus erythematosus (SLE) (30).

Two new vaccines

Two new vaccines received approval from FDA in 2019: Jynneos Smallpox and Monkeypox Vaccine, Live, Non-Replicating from Bavarian Nordic, the only current FDA-approved vaccine for the prevention of monkeypox disease (31), and Dengvaxia from Sanofi Pasteur, the first vaccine approved by FDA for the prevention of dengue disease caused by all dengue virus serotypes in people ages 9 through 16 (32).

References

1. FDA, Novel Drug Approvals for 2019, *www.fda.gov*, accessed Dec. 18, 2019.
2. FDA, Novel Drug Approvals for 2018, *www.fda.gov*, accessed Dec. 18, 2019.
3. Kyoto Encyclopedia of Genes and Genomes Drug Database, "New Drug Approvals in Japan: Drugs with New Active Ingredients," *www.genome.jp.com*, accessed Dec. 18, 2019.
4. Kyoto Encyclopedia of Genes and Genomes Drug Database, "European Public Assessment Reports (EPAR) Authorised Medicine," *www.genome.jp.com*, accessed Dec. 18, 2019.
5. CDSCO, "List of Approved New Drugs," *cdsco.gov.in*, accessed Dec. 18. 2019.
6. Kyoto Encyclopedia of Genes and Genomes Drug Database, "New Drug Approvals in the USA, Europe and Japan," *www.genome.jp.com*, accessed Dec. 18, 2019.
7. M. Kashoki, et. al., *Clin. Pharmacol. Ther.* (July 15, 2019).
8. N. S. Downing, A. D. Zhang, J. S. Ross, *N Engl J Med*. 376:1386-1387 (2017).
9. FDA, "FDA Approves First Therapy to Treat Patients with Rare Blood Disorder," Press Release, Nov. 8, 2019.
10. FDA, "FDA Approves First Therapy for the Treatment of Adult Patients with a Rare Blood Clotting Disorder," Press Release, Feb. 6, 2019.
11. FDA, "FDA Approves New Treatments for Heart Disease Caused by a Serious Rare Disease, Transthyretin Mediated Amyloidosis," Press Release, May 6, 2019.
12. FDA, "FDA Approves First Treatment for Inherited Rare Disease," Press Release, Nov. 20, 2019.
13. FDA, "FDA Approves First Therapy for Rare Joint Tumor," Press Release, Aug. 2, 2019.
14. FDA, "FDA Approves First Targeted Therapy to Treat Patients with Painful Complication of Sickle Cell Disease," Press Release, Nov. 15, 2019.
15. FDA, "FDA Approves First Treatment to Increase Pain-Free Light Exposure in Patients with a Rare Disorder," Press Release, Oct. 8, 2019.
16. FDA, "FDA Approves First PI3K Inhibitor for Breast Cancer," Press Release, May 24, 2019.
17. FDA, "FDA Approves First Treatment for Post-Partum Depression," Press Release, March 19, 2019.
18. FDA, "FDA Approves New Treatment for Hypoactive Sexual Desire Disorder in Premenopausal Women," Press Release, June 21, 2019.
19. FDA, "FDA Approves First Oral GLP-1 Treatment for Type 2 Diabetes," Press Release, Sept. 20, 2019.
20. FDA, "FDA Approves First Treatment for Severe Hypoglycemia that Can Be Administered without an Injection," Press Release, July 24, 2019.
21. FDA, "FDA Approves New Nasal Spray Medication for Treatment-Resistant Depression; Available Only at a Certified Doctor's Office or Clinic," Press Release, March 5, 2019.
22. FDA, "FDA Approves New Drug for Treatment-Resistant Forms of Tuberculosis that Affects the Lungs," Press Release, Aug. 14, 2019.
23. FDA, "FDA Approves New Antibiotic to Treat Community-Acquired Bacterial Pneumonia," Press Release, Aug. 19, 2019.
24. FDA, "FDA Approves New Antibacterial Drug to Treat Complicated Urinary Tract Infections as Part of Ongoing Efforts to Address Antimicrobial Resistance," Press Release, Nov. 14, 2019.
25. FDA, "FDA Authorizes Marketing of First Next-Generation Sequencing Test for Detecting HIV-1 Drug Resistance Mutations," Press Release, Nov. 5, 2019.
26. FDA, "FDA Approves Innovative Gene Therapy to Treat Pediatric Patients with Spinal Muscular Atrophy, s Rare Disease and Leading Genetic Cause of Infant Mortality," Press Release, May 24, 2019.
27. FDA, "FDA Approves First Treatment for Children with Lambert-Eaton Myasthenic Syndrome, a Rare Autoimmune Disorder," Press Release, May 6, 2019.
28. FDA, "FDA Approves First Anticoagulant (Blood Thinner) for Pediatric Patients to Treat Potentially Life-Threatening Blood Clots," Press Release, May 16, 2019.
29. FDA, "FDA Approves First Treatment for All Genotypes of Hepatitis C in Pediatric Patients," Press Release, April 30, 2019.
30. FDA, "FDA Approves First Treatment for Pediatric Patients with Lupus," Press Release, April 26, 2019.
31. FDA, "FDA Approves First Live, Non-Replicating Vaccine to Prevent Smallpox and Monkeypox," Press Release, Sept. 24, 2019.
32. FDA, "First FDA-Approved Vaccine for the Prevention of Dengue Disease in Endemic Regions," Press Release, May 1, 2019. **PT**

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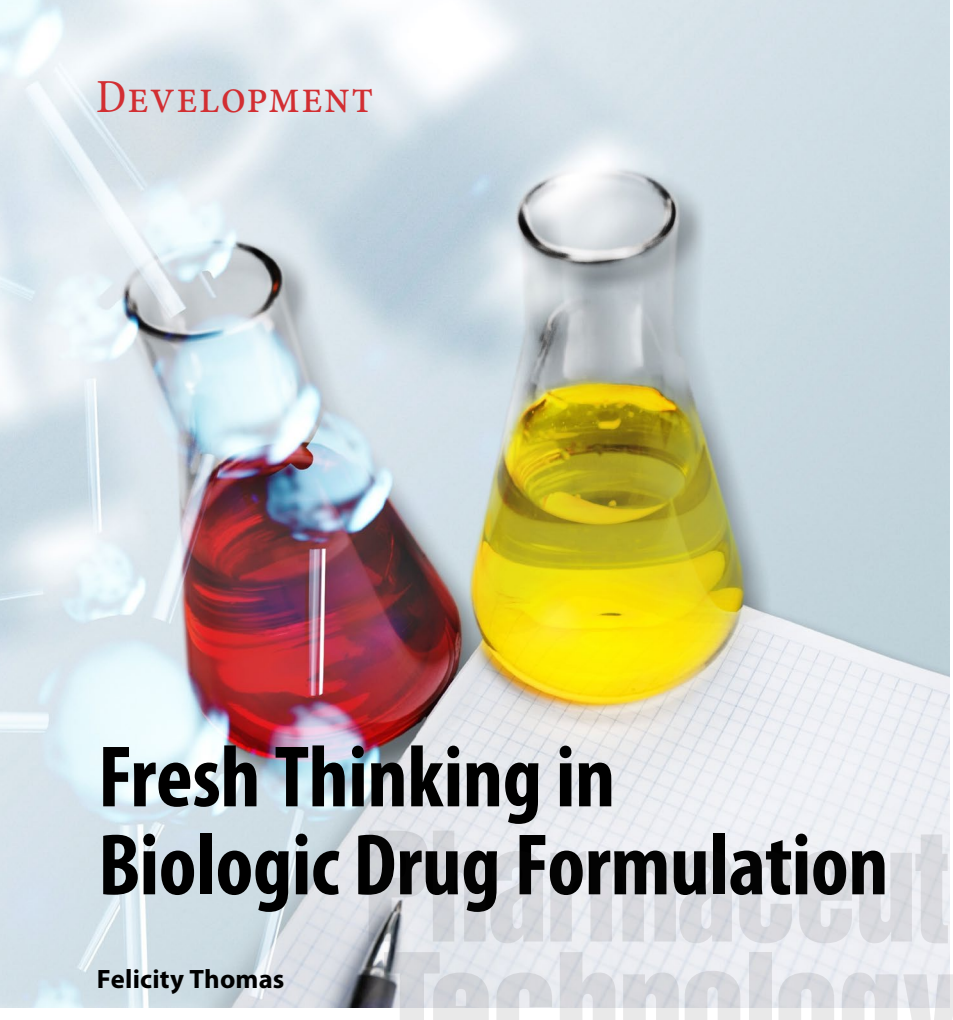

Fresh Thinking in Biologic Drug Formulation

Felicity Thomas

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Biologics raise unique formulation and development challenges, and industry is still on a learning curve to get the best out of these diverse and complex therapies.

The global biologics market has experienced significant growth over recent years and, according to market research, is expected to continue to grow in the near future, potentially being worth $625.6 million by 2026 (1). Advancement of the sector is projected to be driven by an increase in prevalence of chronic conditions, technological advancements, mergers and acquisitions, more market approvals, and the development of more efficient biologics (1).

However, biologics raise unique challenges in formulation and development, not least as a result of the large size of the molecules but also due to other characteristics of the complex API. According to Fran DeGrazio, vice-president, Global Scientific Affairs and Technical Services, West Pharmaceutical Services, the size of biologic drug products is particularly challenging when approaching drug delivery. "To be most effective, biologics must typically be injected directly into the bloodstream," she says. "Additionally, biologics are sensitive to their environment and can easily aggregate or denature, leading to problems such as the formation of particles, which may then be injected into the patient."

"Biological molecules are not only larger in size but also more complex in structure when compared with small molecules," concurs Constança Cacela, director—RD Analytical Development, Hovione. "This structural complexity can lead to challenges in ensuring stability during processing and long-term, which may result in potential losses of activity and increased immunogenicity."

Circumventing phenomena, such as denaturation, aggregation, and other forms of structural change, are of key importance when processing and developing formulations with biological molecules, Cacela further explains. "These aspects of biologics are responsible for an increased difficulty, requiring advanced technical expertise," she says.

Administration: Moving from IV to SC?

When developing large molecule formulations, and depending on the delivery route, there will be different challenges to address with implication on the respective excipient selection, explains Eunice Costa, director—RD Drug Product Development, Hovione. "For injectables, concentration and viscosity of subcutaneous formulations are the main points to address and optimize, whereas for oral enzymatic and acidic degradations low absorption needs to be addressed as well," she says. "Finally, for nasal, the challenge is mainly related with the low absorption while inhalation is targeting the lung."

There has been an upswing in the proportion of drugs in the pipeline to be administered via a subcutaneous (SC) delivery route, with biomolecules that are currently administered intravenously (IV) being formulated for SC instead. "Major issues associated with SC administration for biologics are the small volumes that require high concentrations of the API," Costa adds. "The need for high concentrations results in increases of viscosity and challenges in maintaining isotonicity of the liquid formulation as well as in preventing aggregation. Moreover, viscous formulations are difficult and painful to administer. Addressing these issues includes careful optimization of the excipients in the formulation."

For DeGrazio, there are multiple approaches available for developers of formulations to be administered subcutaneously. "One approach is through optimization of the drug formulation design," she asserts. "This can be accomplished using technologies that

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help the drug meet deliverability criteria for SC injections."

Another approach includes using a suitable delivery device. "An example of this approach may be drugs that are delivered to the patient through wearable injector devices," DeGrazio continues. "Typically, a combination of both formulation optimization, and an appropriate delivery device, facilitates the transition from IV administration to SC."

Alternative routes

The size of biologic drug products—ranging from 3000 atoms to more than 25,000 atoms—has meant that the primary route of administration is via injection, states DeGrazio. "Size is a challenge for crossing the barriers into the body using other routes," she says. "The oral route is preferred for any drug product. However, due to the sensitive nature of active ingredients, they will not survive the acidic pH and digestive enzymes of the stomach. This would be just the initial challenge, the next would be absorption into the bloodstream."

However, there are several benefits in developing biologic formulations for alternative routes of administration, argues Cacela, with probably the most obvious one being improved patient adherence. "In the development pipeline, there are increasing programs in the areas of oral, inhalation, and nasal, with the first one generally being considered as the optimal route," she says.

To overcome the enzymatic and pH-dependent degradation of drugs in the stomach, in addition to permeability issues and the potential for degradation via first pass metabolism, formulation strategies, such as enzymatic activity inhibitors, permeation enhancers, enteric coatings, and carrier molecules, can be employed, Costa reveals.

"The increased focus on inhalation delivery reflects the benefits offered by this route of administration," Costa continues. "Delivery by inhalation bypasses the harsh conditions in the gastrointestinal tract, allowing the administration of lower doses with reduced side effects, particularly for respiratory drugs delivered directly to the site of action."

There has been an upswing in the proportion of drugs in the pipeline to be administered via a subcutaneous delivery route…

For systemic delivery, administering drugs to the lungs can also allow direct absoprtion into the bloodstream, leading to a more rapid onset of action, Costa explains. "The main challenges for inhalation include ensuring that the drug reaches the lung (e.g., delivery efficiency), a limited array of excipients available to interact and stabilize large molecules that are safe in the lung, as well as the lack of permeability to very large biomolecules," she says. "Overall strategies include optimal design of the inhaler device , study of the interactions between excipients and biomolecules, biomolecule engineering (e.g., fragmented antibodies, anticalins) with the purpose of maximizing efficiency."

Nasal delivery, historically, has tended to be used for local delivery of drug substances. However, Costa adds that more recently it is becoming recognized as an interesting route for direct access to the brain. "It has been actively pursued for biologics, in particular peptides, due to the ease of administration," she states. "As opposed to inhalation, one of the major limitations of this route is the relatively limited low surface area available for absorption. To increase absorption, mucoadhesive polymers are commonly added to the formulation."

Cacela emphasizes that an overarching technological solution, useful for overcoming the limitations for the various delivery routes discussed, is the use of particle engineering. "Through the preparation of optimally sized and shaped particles, the bioavailability of the drug can be improved," she says. "As an example, nanoparticle-based delivery systems, such as lipid nanoparticles, are used for improving penetration of large molecules. In addition, these systems provide protection to the drugs, which is particularly relevant for large molecules administered orally."

A common technique used to engineer particles is spray drying, which Cacela states is the most commercially advanced solution capable of preparing stable and effective formulations. "Despite being generally used for oral small molecules, its benefits can be easily expanded to other systems and routes of administration," she adds. "The anticipated forecast growth for spray drying services being applied to biologics (2) is a strong indicator of that."

Reformulation and self-administration trends

SC administration of biologics, in particular antibodies, is a strategy being employed by industry to improve patient comfort and provide pharmacoeconomic benefits (3), highlights Cacela. Highlighting another example (4), she adds that in some cases using SC administration can result in improved safety due to reduced adverse effects. "Besides the aforementioned benefits, reformulation of existing biologics may also be of potential value for the originators as a means of life-cycle managements," she says.

In agreement, DeGrazio notes, "We are definitely seeing the trend towards reformulation as part of lifecycle management to enable self-administration. New biologic drug products in competitive therapeutic categories

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are being introduced in self-administration systems. This is one of the main reasons for the growth of drug-device combination products in the marketplace."

The move toward self-administration is being driven by a number of factors, DeGrazio continues. "One of the most significant is the potential cost savings if the delivery of a drug product can be done at home, versus in a hospital or clinic," she says. "Additional reasons include improved quality of life for patients and product differentiation in a therapeutic category."

Mitigate risks, save costs

The costs associated with any medical therapy are being scrutinized by regulatory bodies, governments, and patients. Biological therapies, due to the molecular complexity and associated challenges during development means that they come with a high price tag.

"One of the best ways to impact costs is by mitigating risks early in the development process," asserts DeGrazio. "Many drug product formulators think that all problems can be solved through their ability to adjust and optimize a formulation. However, not all formulators have a broad understanding of the impact of aspects beyond the drug formulation, aspects of which they need to be cognizant."

Highlighting some examples, DeGrazio notes that formulators must be aware of the potential impact primary packaging may have on the biological drug product. Additionally, whether or not it is possible to use the drug product with a delivery device is an important consideration. "Both packaging and device options are essential when looking at improving the patient experience," she adds.

"The route chosen regarding drug pricing must not inhibit innovation and must ensure economic sustainability," warns Cacela. "However, R&D effectiveness may be improved and, therefore, have an impact on the final cost of biologics."

To improve R&D effectiveness, Costa explains that industry is using many different approaches. "Approaches such as preclinical models that more closely resemble the human conditions to be treated, reducing late-stage (Phase II and III) attrition rates and cycle times during development by using a better model," she says. "New tools and technologies arising from the digital transformation era, such as the application of artificial intelligence algorithms to experimental and clinical data, further improve R&D effectiveness."

Specifically looking at formulation, Costa reveals, "As more biomolecules are screened models can be improved allowing for *in-silico* screening and reducing the chances of failure later on in clinical development."

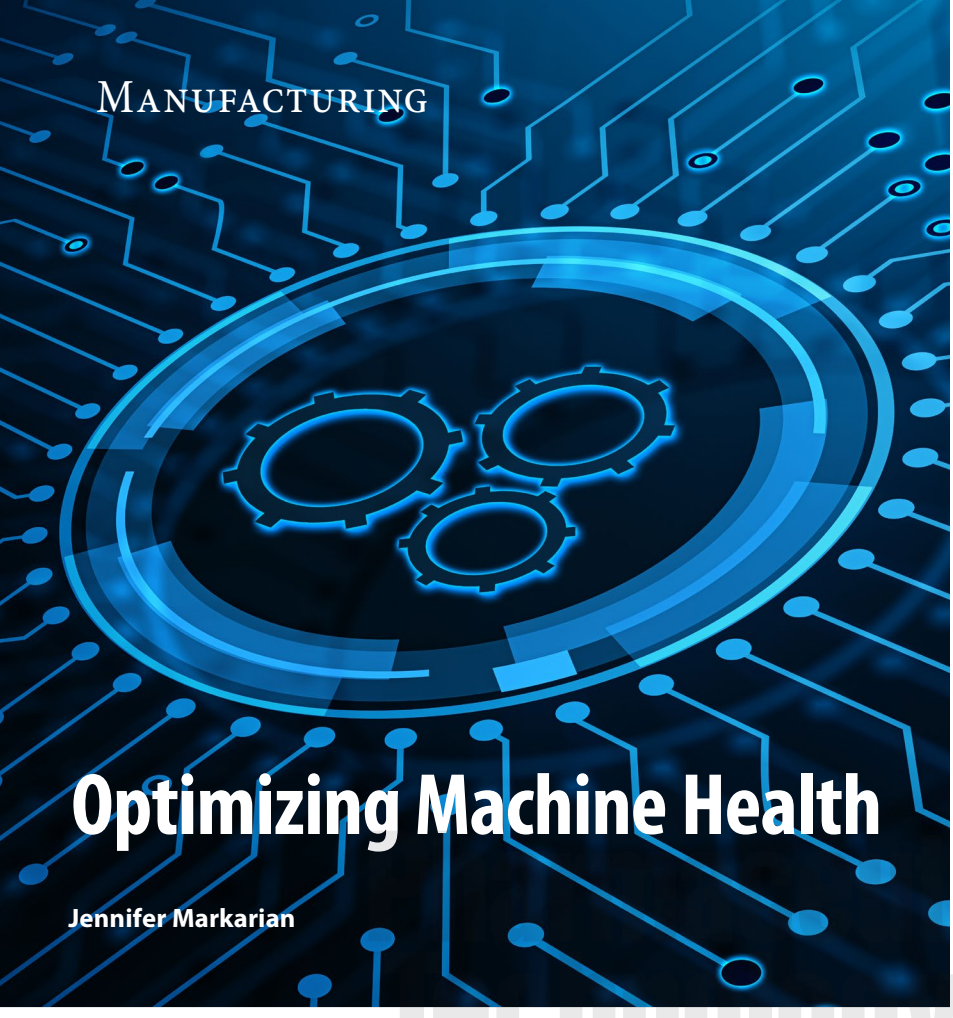
Still on a learning curve

For Cacela there is still much to learn and more development required in both the delivery and formulation of biologics. "Besides this, the diversity of these drugs and therapies is very large and it is difficult to find a common solution even within a same class of biomolecules," she states. "Therefore, the coming years will be marked by advances in the delivery of novel biologics, as well as biosimilars, with new solutions, new excipients, and new delivery support molecules."

"We have learned that the drug formulation itself can have a detrimental impact on the function of a delivery device, such as a prefilled syringe system," adds DeGrazio. "By understanding issues early in the development process, however, downstream problems can be avoided. Partnership with suppliers who are familiar with such challenges can be of great benefit. An openness to engage, and learn from each other, can benefit effective drug development and the patient."

References

1. Reports and Data, "Biologics Market By Product (Monoclonal Antibodies, Vaccines, Recombinant Hormones/Proteins), By Application (Cancer, Infectious Diseases, Autoimmune diseases), By End use (Hospitals, Clinics, Diagnostic Centres), and Region, Forecasts to 2026," Market Report, *reportsanddata.com* (October 2019).
2. Research and Markets, "Pharmaceutical Spray Drying Market (2nd Edition), 2018–2028," Roots Analysis, *researchandmarkets.com* (April 2018).
3. K. Papadmitriou, et al., *Facts Views Vis. Obgyn.*, 7 (3) 176–180 (2015).
4. P. Moreau, et al., *Lancet Oncol.*, 12 (5) 431–440 (2011). **PT**



Optimizing Machine Health

Jennifer Markarian

Data collected through the Industrial Internet of Things enable predictive maintenance.

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Performing equipment maintenance to prevent breakdowns or unplanned process stops is an obvious best practice; how to know when to do that maintenance is not as simple. Preventive maintenance is the conventional pharmaceutical industry practice that involves setting a time-based maintenance schedule for a piece of equipment, typically using models based on experience and original equipment manufacturer (OEM) recommendations. Preventive maintenance schedules are usually set conservatively, to be short enough to have a low risk of failure.

Digital tools are helpful in managing this routine and scheduled maintenance. "Many companies still rely on paper records to manage their manufacturing floors, including equipment maintenance activities. But in a high-paced and high-volume production environment, you simply can't be proactive when you operate on paper," suggests Matt Lowe, MasterControl's president of laboratories. "Digital preventive maintenance systems are the bare minimum in today's competitive manufacturing marketplace. The goal is to avoid missed or delayed maintenance tasks and keep equipment in good working condition," says Lowe.

Some pharmaceutical manufacturing facilities run 24 hours a day, seven days a week, with two-week shutdowns twice a year for preventive checks, notes Jon Biagiotti, product marketing manager at Augury. This standard approach, however, may not be cost-effective or an optimal use of resources. "Preventive maintenance may be done too late, not addressing potential issues until the next scheduled check, so that it degrades to a more expensive fix. Or it may be done too early, when it isn't needed yet," he says.

"The pharmaceutical community is showing great interest in predictive maintenance because the conservative nature of our applications results in frequent preventive maintenance. Preventive maintenance is not always needed and results in costly downtime," adds Pamela Docherty, industry manager at Siemens.

Continuous monitoring and condition-based predictive maintenance offer the potential to improve efficiency and quality compared to time-based preventive maintenance.

Predictive maintenance

Predictive maintenance takes asset health analysis to the next level, by collecting data from equipment using sensors connected through the Industrial Internet of Things (IIoT) and analyzing that data to predict how an asset will perform in the future. Decisions are tailored for a specific situation, rather than following a general expectation.

"In the past, predictive analytics on a set of many assets was too time consuming to be practical, but advanced analytics enables faster, cost-effective insights," explains Michael Risse, vice-president and chief marketing officer at Seeq. Using the IIoT and predictive analytics, "the assets that need attention provide advanced warning on what they will need in terms of spare parts and maintenance in enough time to take action at the best price and timing for the organization."

In many cases, data needed for predictive analytics are already collected and available in historians or other databases, says Risse. If more data are needed, sensors and wireless networks are easily added. The barrier to predictive maintenance is, thus, not the availability of data, but the ability of subject matter experts to leverage the data. "It's the ability to create actionable insights and deliver it through an easy-to-use interface that creates value," notes Risse.

Enabling process engineers to analyze the data themselves, with self-service analytics, gives these experts the knowledge they need to optimize maintenance, says Edwin van Dijk, vice-president of marketing at TrendMiner. Another key to self-service analytics is contextualizing the data coming from the equipment using

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process-related data. "The goal of predictive maintenance is to be able to perform maintenance at a time when it is not only the most cost-effective, but also when it will have the least impact on operations," says van Dijk.

"Human intervention is critical to determine the best course of action based on the available information," adds Lowe. For example, with insight into an upcoming problem, "manufacturers can proactively reassign equipment and divert upcoming batches to other production lines."

Machine learning

Advances in computing power and in artificial intelligence (AI)—particularly machine learning—have enabled predictive maintenance. For example, digital twin libraries (i.e., collections of models) were originally developed by OEMs for specific equipment, and now general models that can be tuned to specific pieces of equipment are increasingly available, says Elinor Price, senior product manager at Honeywell Process Solutions. She says that the role of the asset digital twin is to alert the maintenance team to be proactive rather than reactive. For example, advanced pattern recognition analytics (i.e., machine learning) can identify potential equipment problems by spotting changes in flow or temperature before they are large enough to trigger an alarm on the control system.

"Machine learning algorithms build a model of the machine to learn how it operates," explains Biagiotti. "By comparing current performance to past performance, anomalies can be detected. Full fault diagnostics can be conducted by looking at the frequency spectrum, applying pattern recognition, and comparing signals to similar machines. Based on [these diagnostics], specific, actionable recommendations are made to improve the health of a machine."Machine learning is often based on vibration analysis, but it goes beyond a conventional rules-based system. "The system learns how the machine operates so that you don't receive false alarms," says Biagiotti. "By comparing one machine's data to similar machines, the accuracy improves exponentially as we collect more data. Because the IIoT is being leveraged, manufacturers can benchmark equipment and production lines at a global level, comparing plants around the world."

Use cases

Biagiotti says that one of the main uses of machine learning algorithms is monitoring cleanroom utility equipment, which are especially critical because shutdowns result in the time-consuming and expensive process of reconditioning the cleanroom. Air-handling units, for example, are usually enclosed and difficult to access, but wireless sensors can be placed in the enclosure to send data through the IIoT. In one case, machine learning algorithms identified bearing wear on two air handling units, and correcting the problem prevented an unexpected shutdown.

In another case, vibration analysis was used to detect misalignment and bearing failure on a chilled water system pump. The pump was required to keep a constant temperature for experimental product. "The system detected a failure 120 days in advance, saving batch experiments that, if lost, could have wasted months of time," says Dennis Belanger, director of Operational Certainty Consulting at Emerson.

He reports on another use, "Emerson worked with one organization to develop a machine learning system that could detect sensor drift on a temperature sensor for a heat-treat skid. That implementation detected an aberration 60 days in advance, which allowed the organization to save a batch worth over $1 million."

Heat-exchanger performance is crucial for process control and offers an opportunity for maintenance optimization, says van Dijk. "Fouling of heat exchangers increases the cooling time, but scheduling maintenance too early leads to unwarranted downtime. Scheduling too late leads to degraded performance, increased energy consumption, and potential risks," he explains. "In a reactor with subsequent heating and cooling phases, the controlled cooling phase is the most time-consuming, and it is almost impossible to monitor fouling when the reactor is used for differ-

Design for reliability

Design for reliability (DfR) is a methodology for ensuring that equipment or other assets are built so that they run consistently without unexpected failure, and that they can be accessed and maintained over time. "Asset health accountability drives the creation and execution of a robust reliability framework," says John Ganaway, Design for Reliability practitioner at Jacobs. Software may assist in DfR, but in reality it is the stakeholders who must "build and execute a reliability framework," says Ganaway. *Pharmaceutical Technology* interviewed Ganaway about DfR and its application in pharmaceutical manufacturing.

PharmTech: What is DfR?

Ganaway (Jacobs): DfR aims to ensure reliability, maintainability, ergonomics, accessibility, and availability of assets. The concept blends aspects of statistics, probability, and reliability theory, as well as engineering, analysis, and stakeholder engagement. DfR should be active throughout an asset's or product's lifecycle so that users can evaluate and verify that the equipment has been robustly designed, and so that problems caused by any design issues may be predicted before they can affect performance.

PharmTech: How do new technologies such as AI/predictive maintenance aid in DfR?

Ganaway (Jacobs): System health indicators (SHIs) are crucial. They are based on such process health indicators (PHIs) as pH, conductivity, pressure, temperature, and flow, and then integrated with asset health indicators (AHIs) (e.g., vibration magnitude with frequencies, oil cleanliness such as ISO codes, temperature using thermography, ultrasound using acoustics, current, voltage, and material thickness). With these data, artificial intelligence (AI), using improved data models, can create a method for enunciating defects. Once users are aware of the defects and the probability of their occurring, they can make better design decisions, eliminating those defects at the design stage.

To read the full interview, go to **PharmTech.com/designing-pharma-equipment-reliability**.

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ent product grades and when a different recipe is required for each grade. In one instance, a monitor was set up to look at the cooling times of a company's most highly produced products. If the duration of the cooling phase started to increase, a warning was sent to the engineers who could then schedule timely maintenance, sometimes two to three weeks in advance. The gained benefits are extended asset availability, predictive maintenance leading to operational and maintenance cost reduction, and reduction of safety risk."

Predictive algorithms can also prevent the breakthrough of a filter in a suspension tank, which is used for removing impurities in a product before it is fed into the batch. "Sometimes one of the valves can leak, and gas can enter the system. But sometimes the valve can really be stuck due to solids, and the pressure keeps on building up until the filter eventually breaks," notes van Dijk. "Using self-service analytics, process engineers set up the monitors to identify when the valves were leaking, which could be an early indicator of a filter breakthrough that could contaminate an entire batch. With the predictive monitors, the equipment can be replaced sooner, or the process can be controlled differently."

Belanger concludes, "What all successful examples have in common is that decision makers closely examined critical points of failure in the organization and developed solutions that gave the organization the time it needed to react efficiently but thoughtfully, to drive more positive outcomes overall."

Prescriptive maintenance

Prescriptive maintenance describes a method for automatically scheduling required maintenance based on predictive algorithms. "This type of maintenance requires even more data from many more sources than the 'few' sensors at the equipment. Operational contextual information is required to artificially assess all circumstances to generate the adequate prescription for the maintenance required," explains van Dijk.

"Prescriptive maintenance is being adopted by best-in-class pharma manufacturers to drive better production through more informed decision making," adds Belanger. He explains that this method uses analytics tools to "find patterns or anomalies in large amounts of seemingly unrelated data—understanding and evaluating the performance of a process or system rather than measuring the condition of a single piece of equipment." A corrective action is then "prescribed" to minimize or prevent failure.

The pharmaceutical industry is not ready for a "fully artificial intelligence-led prescriptive analytics system for running an autonomous factory," says van Dijk. "A human-interacted artificial intelligence system is currently a much safer bet." In this system, the process engineers and operators use all the available information to create "process monitors." These automated monitors send "prescriptions" for future maintenance action to the appropriate people or systems in the plant.

Implementation and data integrity

When getting started, companies should first analyze which data are already available and whether existing networks are adequate for data collection. If so, they should move forward with analyzing data, "find the low hanging fruit," and use it to optimize maintenance activities, suggests Donald Mack, industry manager at Siemens.

Quality teams must be educated on the reliability of predictive maintenance, adds Docherty. "It is likely that companies will 'watch' the predictive maintenance data and get an understanding, while slowly pushing the time interval between each predictive maintenance," she says.

Data integrity is crucial for IIoT-connected equipment. "Digitalization and cybersecurity go hand in hand. What were once isolated, nearly impossible to access devices are now being brought on to the information superhighway," says Mack.

"A strong IIoT solution requires a detailed, security-driven system architecture that can effectively represent multi-layered security within the solution," adds Brycen Spencer, IoT consultant at Siemens. "Companies should seek a solution designed to be scalable, resilient, and efficient. Features such as strict access management, encryption, network security, tenant and environment separation, and filtered communication channels are fundamental to good IIoT architecture." **PT**

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Data analysis methods

For both predictive and prescriptive maintenance, understanding the process, building data models, and analyzing the data are key, says Edwin van Dijk, vice-president of marketing at TrendMiner. Subject matter experts—the process engineers—can use "self-service analytics" tools to search and filter data, perform root cause analysis, test hypotheses, and build monitors to predict process and equipment performance. Van Dijk explained three ways to analyze data using this self-service analytics approach.

"The first is event-based. If a certain signature behavior is detected that can affect another part in the process that typically occurs later, a notification can be generated. This notification can include instructions for the required preventive actions or required maintenance.

"The second is probabilistic. The current behavior is interpreted, and a likeliness of future behavior is calculated, optionally resulting in automatically scheduled maintenance work orders with the needed instructions.

"The third type is regressive. The prediction is based on certain conditions that must be met and verified, and in case of deviations, the instructions can be given to the control room, or maintenance can be scheduled for the near future.

"For all three situations, the events can be captured in case they occur, providing more information for improving future predictive and even prescriptive maintenance work."

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Self-Guided Control of a Fluid Bed Granulation Process

Caroline McCormack, Chris O'Callaghan, Gareth Clarke, Ian Jones, Luke Kiernan, and Gavin Walker

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Advanced dynamic process control using PAT data improves product quality.

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Globally, there is an increasing trend toward the use of Industry 4.0 principles, with the Industrial Internet of Things (IIoT) being a key component, while regulators are actively encouraging pharmaceutical companies to modernize their approaches to drug development and manufacturing to deliver higher quality products. Better process understanding, drug product development, and manufacturing throughout the commercial lifecycle of drug products will lead to faster time-to-market and a more reliable, predictable supply chain (1).

Adopting several of the tools and technologies which are part of the current Industry 4.0 revolution (e.g., process analytical technology [PAT], big data analytics, manufacturing intelligence, in-process control, and cloud architecture) into everyday pharmaceutical product development and commercial manufacturing may provide an effective solution to many manufacturing quality challenges. Adoption of these technologies would also dramatically improve productivity while maintaining competitive advantage and reducing costs for the manufacturer (2,3).

This article presents a practical application of Industry 4.0 architecture with commercially available technology solutions and demonstrates how the system can be implemented to reduce risks associated with traditional fluid-bed granulation manufacturing processes.

Fluid-bed wet granulation involves agglomerating a mix of dry primary powder particles (APIs and excipients) by the addition of a granulating solution in a fluid-bed granulator. In the subsequent drying phase, control is crucial because over-drying can lead to increased attrition and fracture of the product, while insufficient drying can result in bed stalling, poor flow, and product stability issues (4). The traditional control approach is recipe driven and largely operator dependent, with minimal provisions for the impacts of raw material or atmospheric variations, both of which are known to affect final granule properties (5).

The automated approach described in this article resulted in greater in-process control and repeatability as well as less batch-to-batch variation. The controller design presented here is intended as a novel example to highlight the flexibility and potential when developing this type of automated, control-driven approach.

Materials and equipment

Formulation. A placebo formulation was used for all batches. It consisted of a mixture of lactose (1 kg Pharmatose 200M, DFE Pharma) and microcrystalline cellulose (0.5 kg AvicelPH-101 NF, DuPont). The liquid binder was an aqueous solution of polyvinylpyrrolidone (1 L, 5.8% w/w, Plasdone K-90, Ashland). Materials were supplied by IMCD Ireland.

Process equipment. Fluid bed granulation was performed in a granulator (Glatt GPCG2) equipped with a particle analyzer (Eyecon$_2$, Innopharma Technology) and near infrared (NIR) spectrophotometer (Multieye$_2$, Innopharma Technology) measuring particle size distribution and product moisture content, respectively. The equipment is shown in **Figure 1**. The automated process control platform

Caroline McCormack is process laboratory manager; **Chris O'Callaghan** is head of engineering, ocallaghanc@innopharmalabs.com; and **Gareth Clarke** is Multieye Product Manager, all at Innopharma Technology, Dublin, Ireland. **Prof. Ian Jones, PhD,** is CEO of Innopharma and Innopharma Education, Dublin, Ireland; **Luke Kiernan** is a PhD student at the Technological University Dublin in Ireland; and **Gavin Walker, PhD,** is professor and director of the Synthesis and Solid State Pharmaceutical Centre at the University of Limerick in Ireland.

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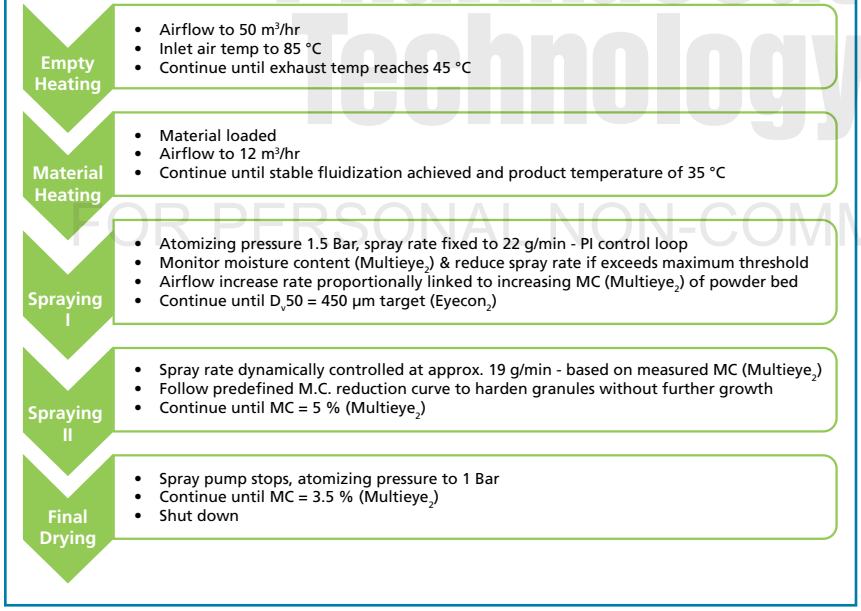
Figure 1. Fluid-bed granulator (Glatt GPCG2) equipped with a particle analyzer (Eyecon2, Innopharma Technology) and near infrared spectrophotometer (Multieye2, Innopharma Technology) with a system user interface (SmartX, Innopharma Technology).

Figure 2. Flow diagram demonstrating key set points and endpoint criteria for each of the phases within the controller. PI is proportional integral control; MC is moisture content.



(SmartX, Innopharma Technology) provided time-aligned data aggregation of process parameter data, PAT data, and environmental sensor data.

Controller development

Controller development is complex and requires a thorough understanding of the process, including critical process parameters (CPPs), their impact on critical quality attributes (CQAs), and the required process specifications. In this case, information on the process design space and optimum control was derived from retrospective analysis of more than 160 batches run on the test-bed system (SmartX Innopharma Technology), while further detailed experimentation was performed to quantify the differences in end-product quality between the results of this advanced dynamic process control (ADPC) approach and the results using a traditional control approach.

The first step in the development was to clearly define the control logic for each process phase. This included identification of key dynamic control relationships, establishing fixed set-points as well as phase and process endpoint criteria. Once configured, this flexible control logic was then implemented and executed via a process-centric scripting environment within the integrated ADPC module.

Throughout the process, real-time PAT data and process sensor data from the fluid-bed system and environmental systems provided a continual input feed to the controller. The controller used this information to make scenario-based decisions on how to respond to process deviations as well as required process changes, including phase changes and endpoint detection.

For the ADPC example presented in this article, five process phases were defined: empty heating, material heating, spraying I, spraying II, and final drying. **Figure 2** describes the five process phases and their corresponding key set-points and endpoint criteria.

Spraying is divided into two phases to demonstrate how PAT measurements may be implemented to achieve in-process control. Additionally, the two phases are designed with the intention to help mitigate against product attrition as typically observed during final drying, thus delivering more consistent endpoint particle size with less batch-to-batch variation. Spraying I is defined by rapid wetting and maximum growth, while Spraying II is defined by further hardening of the granules through reduced spray rate and increased moisture removal to mitigate against product attrition during the drying phase.

A specific moisture-content reduction rate was empirically determined to achieve a quasi-stable median volume distribution (D_v50) particle size while allowing for faster control reaction and, therefore, minimized process deviations as compared to controlling directly based on particle size.

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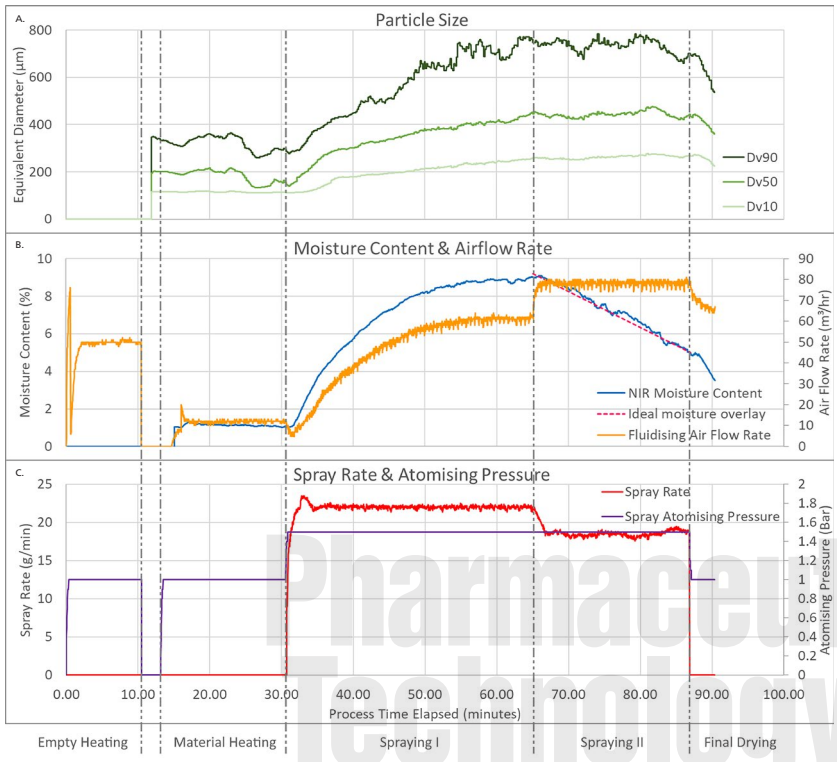
Figure 3. Advanced dynamic process control controller process profiles. NIR is near infrared spectrophotometer; D_v10, D_v50, and D_v90 are volume-based particle-size distributions containing 10, 50, and 90%, respectively.



Results and discussion

ADPC controller. The series of CQA and CPP profiles shown in **Figure 3** are taken from one of the fluid-bed granulation processes executed by the ADPC controller that was developed; these profiles demonstrate the control method's capabilities.

Dynamic control relationships. The key relationship between spray rate and D_v50 particle size can be observed between **Figure 3a** and **3c**. The controller sets the D_v50 particle size target to 450 µm for the duration of spraying and uses real-time particle size data, as measured by the Eyecon$_2$, to monitor the growth profile. During Spraying I, a fixed spray rate is maintained for rapid moisture addition and growth until the target particle size is reached. On entering Spraying II, the target particle size is maintained by following the empirical target moisture-content profile.

This profile is maintained by dynamic control of the spray rate based on real-time moisture content data. Comparing **Figure 3b** and **3c**, modulation of the spray rate after a brief delay can be observed in response to small deviations of the moisture content trend either above or below the target moisture content profile (see **Figure 3b**, dashed line labeled ideal moisture overlay). This process slowly dries the granulate to 5%, which is the trigger to transition to the final drying phase.

Another novel aspect of this control approach can be observed in **Figure 3b**, where the effect of linking air flow rate to moisture content during the Spraying I phase can be seen. This approach allows optimum fluidization to be maintained while the bed becomes heavier and more cohesive, avoiding both the attrition and efficiency impacts of over-fluidizing, and the under-fluidizing risk of bed-stalling.

End-product quality. Endpoint D_v50 particle size values from a number of granulation batches manufactured with the ADPC controller were compared to the endpoint D_v50 particle size values from earlier batches manufactured using a non-ADPC controlled, recipe-driven approach. A significant difference in endpoint product consistency is apparent between the two approaches.

Figure 4a illustrates a significantly wider distribution of endpoint Dv50 particle sizes for batches manufactured via the non-ADPC controlled approach, with variation of 171 µm from the smallest to largest Dv50 value. Comparing batches manufactured with the ADPC controller, a tighter distribution in endpoint Dv50 particle size values is evident, with variation of only 46 µm reported from smallest to largest D_v50 value. These results demonstrate the consistency in batch-to-batch particle size that can be achieved by implementing such a control approach within a fluid-bed granulation process. The ability to achieve greater particle size control via the ADPC controller approach leads to more consistent endpoint particle size and less variation between batches.

Endpoint moisture content values analyzed using the at-line loss-on-drying (LOD) methodology were compared for both control approaches. There is a significant difference in the endpoint LOD values for both of these approaches, primarily due to the non-ADPC controlled approaches using product temperature as an indication of endpoint rather than in-line moisture measurement. The resulting over-drying of the non-ADPC batches is a source of energy waste and possible attrition of the end-product material. Additionally, the ability to reliably fall within, but at the upper end, of a moisture specification helps to improve overall product yield.

Figure 4b clearly demonstrates this variation with a much wider distribution of final LOD values evident for the non-ADPC controlled batches. The total spread of moisture content values is 0.48% for these batches, compared to only 0.16% for the ADPC-controlled batches, which demonstrate much tighter control. These results

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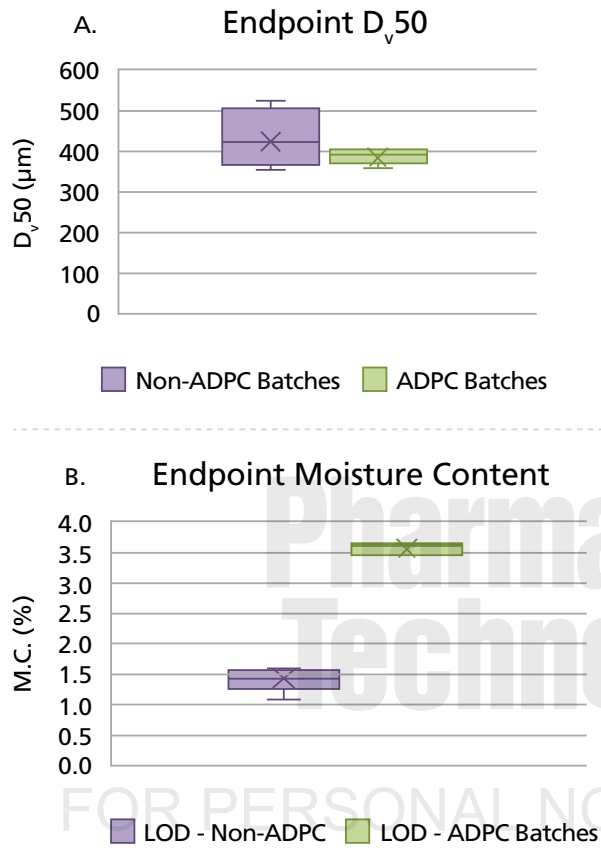
Figure 4. Endpoint material comparisons of (a) median particle size volume distribution (D_v50) for batches made with advanced dynamic process control (ADPC) and with conventional control and (b) moisture content; LOD is loss on drying.



demonstrate the benefit of the in-line NIR moisture-content endpoint detection method.

Endpoint moisture content of the fluid bed granulation process is critical to final product quality and process performance and must be tightly controlled to avoid issues with downstream processing, product dissolution, and stability as well as drug absorption rates in the body. Implementing an ADPC approach can reduce batch-to-batch variation and improve batch repeatability and quality.

Conclusion

The ADPC-controlled approach to fluid bed granulation was shown to produce more consistently sized granules with less batch-to-batch variation when compared to granules produced from a non-ADPC controlled process. In addition, endpoint LOD analysis for the ADPC batches showed significantly less variation and greater consistency. Overall, high process repeatability and reproducibility were demonstrated across multiple, successfully manufactured fluid-bed granulation batches.

The real-time measurements of particle size and moisture content allowed the ADPC controller to effectively determine phase-end criteria. It was further shown to be possible to dynamically manage spray rate, thus ensuring a predetermined moisture content profile was followed by leveraging the NIR moisture-content data.

Finally, the addition of PAT and its integration into the process control strategy dramatically reduces the need for at-line sampling and testing associated with more traditional granulation approaches, as well as reducing the risks associated with human error.

References

1. L. Kiernan, "The Role of Smart Manufacturing in Enabling QRM and KM to Realize Safer and More Affordable Products for Patients in the 21st Century," in *An Audience with Pharmaceutical Regulators, Academia and Industry* (TU Dublin Academic Press, Dublin, 2019), pp. 65–74.
2. T. Dedeurwaerder, et al., "How Data is Changing the Pharma Operations World," *Mckinsey.com*, August 2018.
3. R. Gaertner, "Pharma 4.0—Time to Rethink Manufacturing and Quality," *Manufacturingchemist.com*, January 13, 2016.
4. R. Mattes et al., "In-line Process Analysis of Residual Moisture in a Fluid Bed Granulator-Dryer Using NIR Spectroscopy," *Pharmaceuticalonline.com*, Jan. 2005.
5. T. Lipsanen, et al., *Int. J. Pharm.*, 357 (1-2) 37-43 (2008). **PT**

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A Q&A

Global Health Engagement and Ebola Response Efforts in Uganda

Lieutenant Colonel Mariano Mesngon
Joint Product Manager
Joint Project Management Office for Chemical, Biological, Radiological, and Nuclear Medical

Insights, challenges, and recommendations associated with global health engagement and Ebola response efforts in Uganda.

According to the U.S. Department of Defense's Joint Program Executive Office for Chemical, Biological, Radiological, and Nuclear Defense (JPEO-CBRND), an average of 100 infectious disease outbreaks occur worldwide each day—and most countries are not prepared to respond.[1] So when a recent Ebola outbreak threatened to spread from the Democratic Republic of Congo to neighboring African nations, the JPEO-CBRND spearheaded the Department of Defense's response, supporting local efforts to contain the disease while gaining valuable insights into how to protect the warfighter.

Lieutenant Colonel (Lt. Col.) Mariano Mesngon was stationed as a Department of Defense liaison officer in Uganda to assist in the country's response and preparedness efforts. Now, in his capacity as a joint product manager within the Joint Project Management Office for Chemical, Biological, Radiological, and Nuclear Medical (JPM CBRN Medical), he continues his work, focusing on the advanced development of vaccine programs to protect the warfighter.

Pharmaceutical Technology spoke with Lt. Col. Mesngon about JPM CBRN Medical's mission, his role in Uganda, and how lessons learned in-country pay dividends far and wide today.

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PharmTech: Can you explain what the Joint Project Manager for Chemical, Biological, Radiological, and Nuclear Medical (JPM CBRN Medical) is and your current role in the organization?

Mesngon: The Joint Project Manager for CBRN Medical is one of three Joint Project Managers within the JPEO-CBRND. We are a Department of Defense acquisition organization that provides U.S. military forces and the nation safe, effective, and innovative medical solutions to counter chemical, biological, radiological, and nuclear threats. We envision a U.S. military force that has full medical countermeasure capability to fight and win in the CBRN multi-domain battle space worldwide.

PharmTech: How did you become involved in global health engagement in Uganda?

Mesngon: The JPM CBRN Medical has an in-country research platform called the Joint Mobile Emerging Disease Intervention Clinical Capability (JMEDICC) that conducts clinical trials in an outbreak setting. I assumed the role of Assistant Product Manager for the JMEDICC leadership and served as the government representative for our organization. Honestly, I did not know that I was getting into what was called "global health engagement."

I participated in many working groups and meetings hosted by the Ugandan Ministry of Health that were attended by representatives from many international organizations like the World Health Organization (WHO), the United

Nations International Children's Emergency Fund (UNICEF), Doctors Without Borders, and U.S. government organizations like the Centers for Disease Control and Prevention (CDC) and the U.S. Agency for International Development (USAID). I was usually the only Department of Defense participant, and within the first week or so, it became obvious to me that I was participating in global health engagement activities.

PharmTech: As a U.S. Army officer and a biochemist by training with a Ph.D. in biology, how did your education and/or military training assist you in your assignment in Uganda?

Mesngon: I am an active duty Army officer, and the Army expects its officers to be adaptable leaders and provides us with training, mentorship, and opportunities to develop. I quickly assessed my new environment, integrated quickly into the various teams, and provided assistance and operational planning that the Army emphasizes. As a scientist, I was able to grasp the technical aspects of the task at hand, which was to assist the Ugandan government in developing its Ebola response plan.

PharmTech: What were some challenges faced during the Ugandan efforts?

Mesngon: The main challenge for my organization's perspective was ensuring that the Ugandan government understood how the JMEDICC could assist in preparing for and responding to an Ebola outbreak in the country. The JMEDICC's mission is to conduct clinical trials and their funding restricts them to that task. The Ugandan government saw the JMEDICC as a national asset with the capability to provide Ebola treatment unit services in the event of an outbreak.

In establishing the JMEDICC mission at the Ugandan Fort Portal Regional Referral Hospital, Biodefense Therapeutics—which is the program office with oversight of the JMEDICC—modernized the hospital's core lab, improved hospital power generation and hazardous waste material disposal facilities, and built a well-equipped six-bed, high-containment treatment facility. Additionally, the JMEDICC hired and trained local health care providers that are subject matter experts on treating patients with highly infectious diseases like Ebola.

The issue was that the Department of Defense funds all of that capability with research and development dollars. The Biodefense Therapeutics Program Office, higher levels within the Department of Defense, and the U.S. Embassy, to name a few, coordinated tightly to ensure that JMEDICC activity supporting the Uganda preparedness and response goals were aligned with mission funding.

PharmTech: What lessons learned from your deployment do you apply to your duties at the JPM CBRN Medical? How did your experience in Uganda tie back to both JPEO-CBRND and JPM CBRN Medical's mission of protecting the warfighter?

Mesngon: From a programmatic perspective, my experience in Uganda gave me insight into what type of coordination organizations must accomplish to conduct clinical trials in a foreign country. As a U.S. government agency, I learned how we should coordinate our efforts with the U.S. Embassy and leverage the other U.S. agencies within country teams. Many of the products I am responsible for developing would benefit from the clinical trial in a country like Uganda.

I now have a better understanding of the coordination that is required to perform clinical trials in a foreign country and will factor these into my development plans and resource alignment. The JMEDICC's efforts in Uganda immediately support the needs of the local population in a medical emergency, but it is ultimately providing key data to achieve U.S. Food and Drug Administration (FDA) approval for medical countermeasures that will protect the warfighter.

PharmTech: Given your experience in Uganda, what recommendations would you make if you had to provide assistance for a response effort?

Mesngon: Every good plan starts with understanding the operational environment: engage the U.S. Embassy staff as early as possible and understand how other organizations conduct their clinical trials (if any); reach out to these organizations and adopt their framework to fit our needs; and leverage existing U.S. government assets to the fullest extent possible.

For example, the JPM CBRN Medical's collaboration with the U.S. Navy's Austere Environment Consortium to Enhance Sepsis Outcomes (ACESO) allowed us to quickly establish the JMEDICC in Uganda. Another recommendation would be to explore collaboration with other non-governmental organizations like Doctors Without Borders because they operate in several countries and are trusted partners with local governments.

Reference

1. "JPEO-CBRND Supports International Partners in Congo Ebola Outbreak," Jan. 16, 2019, www.jpeocbrnd.osd.mil/team/news-story/2019/01/16/jpeo-cbrnd-supports-international-partners-in-congo-ebola-outbreak

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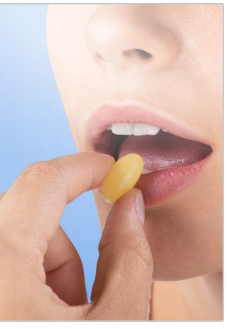

Development of Taste-Masked Oral Reconstitutable Suspension of Cetirizine Dihydrochloride

Gayatri C. Patel

Cetirizine dihydrochloride (CTZ) is a second-generation piperazine derivative, a potent H1 selective antihistaminic agent. Its extreme bitter taste results in poor patient compliance. The aim of this study was to prepare taste-masked drug-resin complex (DRC) using ion exchange resin Kyron T-134. The DRC was evaluated for effect of variables such as resin ratio, pH, temperature, soaking time of resin, and stirring time on drug loading and taste. Reconstitutable suspension was prepared using drug-resin complex and other pharmaceutical excipients in suspension. Formulated reconstitutable suspension was evaluated for parameters before reconstitution, such as flow properties and drug content, and after reconstitution, such as aesthetic appeal, sedimentation rate, redispersibility, particle size, viscosity, pH, drug content, and *in-vitro* dissolution study. During the evaluation period of 14 days, no significant change was observed in pH, viscosity, particle size, and drug content. From the results, it is concluded that effective taste masking of CTZ was achieved using Kyron T-134 and successfully evaluated in reconstitutable suspension.

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A pharmaceutical suspension is a coarse dispersion in which insoluble solid particles are dispersed in a liquid medium (1). FDA's Center for Drug Evaluation and Research (CDER) denotes reconstitutable suspension as "Powder, For Suspension", defined as an intimate mixture of dry, finely divided drugs and/or chemicals, which, upon the addition of suitable vehicles, yields a suspension (2). Reconstitutable suspension is reconstituted at the time of use and thus can be used as liquid formulation, which avoids swallowing problems. In aqueous solutions, many drugs degrade. Moreover, liquid product stability in tropical countries poses a great challenge because these products are exposed to elevated temperatures (up to 40 °C) and high relative humidity (up to 90%), especially during transport and storage (3,4).

Cetirizine dihydrochloride (CTZ) has a bitter taste and is prescribed extensively in both solid and liquid dosage forms for treating allergic conditions, including rhinitis and chronic urticarial (5). Its extreme bitter taste results in poor patient compliance in pediatric and geriatric patients. For these patients, drugs are commonly provided in liquid dosage forms, such as solutions, emulsions, and suspensions (6).

Ion exchange resins are solid and suitably insolubilized high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium reversibly and stochiometrically. They are available in desired size ranges. Bitter cationic drugs can get adsorbed onto the weak cation exchange resins of carboxylic acid to functionally form a complex that is non-bitter. Further, resinates can be formulated as lozenges, chewing gum, suspension, or dispersible tablets and can mask the taste (7,8). Drugs can be bound to the resin by either repeated exposure to or prolonged contact with the resin. Drugs are attached

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Table I. Formulation of cetirizine dihydrochloride (CTZ) oral reconstitutable suspension.

Ingredients	Functional category	mg/5 mL
Drug-resin complex (equivalent to 10mg/5 mL of CTZ)	Taste-masking drug	55
Xanthan gum	Suspending agent	30
Microcrystalline cellulose	Suspending agent	30
Propyl paraben	Preservative	20
Orange flavor	Flavor	25
Titanium dioxide	Opacifier	12
Sucrose	Filler	50

to oppositely charged resin substrates or resinates through weak ionic bonding so that dissociation of the drug-resin complex (DRC) does not occur under salivary pH conditions. This suitably masks the unpleasant taste and odor of drugs (9). The objective of this study was to mask the bitter taste of CTZ using ion exchange resin Kyron T-134 and check the feasibility of incorporating the DRC into reconstitutable suspension to increase patient compliance.

Materials and method

Materials. CTZ was received from UCB India Private Limited (Vapi, India). The resin, Kyron T-134 (Batch no. 3009022), was procured from Corel Pharmachem (Ahmadabad, India). Xanthan gum, microcrystalline cellulose PH101, aspartame, sucrose, propyl paraben, and orange dry flavor were obtained from S.D. Fine Chemicals, Mumbai, India. Deionized distilled water was used throughout the study.

Preparation of DRC. DRCs were prepared by reacting CTZ with cation exchange resin Kyron T-134 in various stoichiometric ratios (1:1, 1:2, 1:3, 1:4, and 1:5). Kyron T-134 as weight ratio of the drug was placed in a beaker containing a required quantity of deionized water and allowed to swell. Accurately weighed CTZ was added to the solution and stirred. The mixture was filtered using Whatman filter paper, and residue was washed three times with 75-mL deionized water each time and dried. Drug in complex was calculated as drug-loading efficiency. DRC was optimized for various process conditions like drug-to-resin ratio, effect of pH, effect of temperature, effect of soaking time of resin, and effect of stirring time (8,10).

Evaluation of DRC

Percentage yield. Percentage yield of DRC was calculated by practical yield divided by actual theoretical yield (11).

Drug content. The CTZ content was determined by dissolving 100 mg of DRC with continuous stirring in 100 mL 0.1 N hydrochloric acid (HCl) (pH 1.2) for 4 h. The solution was filtered. After suitable dilution, the drug content was determined at 231.5 nm by ultraviolet-visible spectrophotometry (UV/Vis). The UV/Vis readings were taken in triplicate. Drug content was calculated using **Equation 1**:

Theoretical concentration of CTZ = 1000 µg/mL

$$\% \text{ drug content} = \frac{\text{practically obtained CTZ concentration}}{1000} \times 100 \quad \text{[Eq.1]}$$

Physical properties of DRC. Physical properties of DRC, such as particle size, angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio were determined. All parameters were performed in triplicate (12,13).

***In-vitro* drug release study.** Drug release from DRC (optimized drug: resin ratio of 1:3.5) in 0.1 N HCl was determined using a *United States Pharmacopeia* (*USP*) XXIV type II (paddle type) dissolution apparatus. DRC equivalent to 10 mg of drug was weighed accurately and added to 900 mL 0.1 N HCl and maintained at 37 °C. Drug release was performed at 100 rpm for 30 min. Five-milliliter samples were withdrawn after every five minutes up to 30 minutes. Samples were filtered with Whatman filter paper no. 41 and were analyzed at 231.5 nm by UV/Vis (12). The readings were taken in triplicate.

Characterization of DRC

Infrared study. The drug, resin, and DRC were subjected to Fourier transform infrared (FTIR) studies to check any drug–resin interaction. FTIR spectra were recorded on samples prepared in potassium bromide using FTIR-8400S with infrared (IR) solution software (Shimadzu, Germany). Data were collected over a spectral region from 4000 cm^{-1} to 400 cm^{-1} (11).

Preparation of oral reconstitutable suspension. The oral reconstitutable suspension of CTZ was prepared from the optimized DRC. The formula is presented in **Table I**. All the ingredients for suspension were sieved through mesh no. 40 to make uniform particle size dispersion. The DRC equivalent to 10 mg/5 mL of suspension was mixed with the excipients. They were mixed properly to ensure uniform dispersion. Evaluation was performed on parameters before and after reconstitution (14,15).

Evaluation of oral reconstitutable suspension. Dry powder blend, ready for reconstitution, was evaluated for flow properties and drug content. After reconstitution, different pa-

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Table II. Preliminary trials for optimization of drug:resin ratio.

Drug:resin ratio	% Drug loading
1:1	70.56±1.14
1:2	73.42±1.03
1:3	78.56±1.14
1:3.5	85.04±0.87
1:4	84.57±0.85

Table III. Pre-reconstitution evaluation of dry powder blend.

Test	Test results
Bulk density (gm/cc)	0.875
Tapped density (gm/cc)	0.983
Compressibility index (%)	11.41
Hauser's ration	1.12
Angle of repose (θ)	29.56
Drug content (%)	98.26±0.526

rameters, such as sedimentation volume, redispersibility of suspension, viscosity, pH, drug content, and *in-vitro* drug release study were evaluated (10,16).

Sedimentation volume and redispersibility of suspension. The formulated suspension was evaluated for physical stability by determining the sedimentation volume. Fifty milliliters of suspension was taken in a 100-mL stoppered graduated measuring cylinder. The suspension was dispersed thoroughly by turning the measuring cylinder upside down three times. Later, the suspension was allowed to settle for three minutes, and the volume of sediment was noted. This is the original volume of sediment (H0). The cylinder was kept undisturbed for 14 days. The volume of sediment was read at day 0, at day 7, and at day 14. The day 14 reading was considered the final volume of sediment (Hu) (**Equation 2**). The redispersibility of the suspension was checked by repeatedly turning the stoppered cylinder upside down until there was no sediment at the bottom of the cylinder.

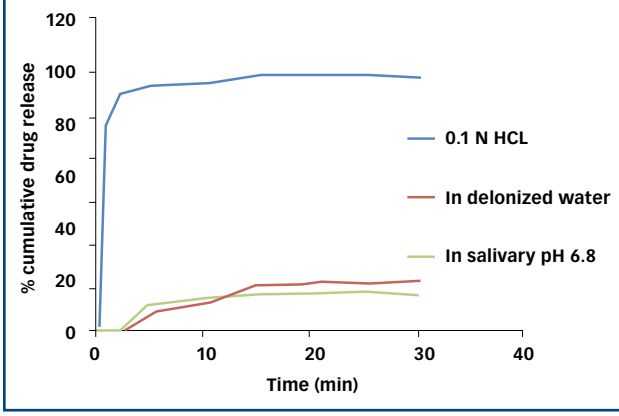
$$\text{Sedimentation volume} = \frac{H_u}{H_0} \quad \text{[Eq.2]}$$

Determination of viscosity. A viscosity study was performed using a Brookfield viscometer DV-II+Pro, USA (Spindle no. S61). Viscosity was measured at 100 rpm, at 25 °C. The limits on viscosity were selected such that the suspension reached a physically stable state.

pH of the suspension. pH of the suspension was determined using a digital pH meter.

Assay of suspension. Five milliliters of suspension were taken in a 50-mL volumetric flask, and the volume brought up to 50 mL with 0.1 N HCL. The solution was sonicated for 30 min and filtered. Absorbance was then measured at wavelength 231.5 nm in UV-Vis, after which the percentage drug content was calculated.

Figure 1. *In-vitro* drug release profile of drug-resin complex in different dissolution media. HCl is hydrogen chloride.



***In-vitro* drug release.** *In-vitro* drug release of the suspension was performed using USP-type II dissolution apparatus (paddle type). The dissolution medium of 500 mL 0.1 N HCL was placed into the dissolution flask and temperature was maintained at 37±0.5 ºC at 100 rpm. Five milliliters of suspension solution was placed in each flask of the dissolution apparatus. The apparatus was allowed to run for 35 minutes. Samples measuring 10 mL were drawn after every 5 min, 10 min, 15 min, 20 min, 25 min, 30 min, and 35 min. The fresh dissolution medium was replaced every time with the same quantity of the sample. Collected samples were suitably diluted with 0.1 N HCL and analyzed at 231.5 nm using 0.1 N HCL as blank. The cumulative percentage drug release was calculated.

Results and discussion

Drug loading. As presented in **Table II** the complexation of drug with Kyron T-134 in a weight ratio of 1:3.5 gave efficient drug loading. The stirring time for all subsequent complexation processes was fixed to 4 h. Stirring time between 4 h and 5 h showed no significant change. The pH and temperature of solution did not show any significant effect on drug loading. Therefore, pH 4 and room temperature were selected for optimized batch preparation. No significant difference was observed when soaking time of resin in deionized water was changed from 30 min to 120 min. Thus, the soaking time of resin in deionized water was fixed to 30 min. Optimum conditions for the preparation of DRC were selected and used for further studies.

Micromeritics. The bulk and tapped densities were found at 0.613±0.013 and 0.674±0.016 g/cc, respectively. The compressibility between 5%–12% indicates excellent compressibility. The values of Hausner's ratio at less than 1.25% and angle of repose below 30° indicates good flowability.

***In-vitro* drug release from DRC. Figure 1** demonstrates the drug release studies of CTZ from the DRC in 0.1 N HCl, phos-

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Table IV. Sedimentation study of suspension. Hu is sedimentation volume at 14th day. H0 is original sedimentation volume at 0 day.

Test	H_u	H_o	Sedimentation volume (H_u/H_o)
1 h	48	50	0.96
7 days	40	50	0.8
Hauser's ration	32	50	0.64
Angle of repose (θ)		29.56	
Drug content (%)		98.26±0.526	

Table V. Evaluation parameters of after-reconstitution oral suspension.

Sample no.no	Test	0 day	7 days	14 days
1	Appearance	Uniform	Uniform	Uniform
2	Taste	Uniform	Uniform	Uniform
3	pH	6.8±0.1	6.7±0.1	6.7±0.1
4	Viscosity (cps)	56	52	50
5	Particle size	265±55	268±45	272±48
6	Drug content	98.45±0.521	98.012±0.865	98.32±0.601

phate buffer pH 6.8, and deionized water. In 0.1 N HCl more than 90% of drug release was achieved in 5 min, whereas in phosphate buffer pH 6.8 and deionized water, less than 20% drug release was achieved in 30 min. The exchange process of drug release is shown in **Equation 3**:

$$Resin^- - Drug^+ + X^+ \rightarrow Resin^- - X^+ + Drug^+ \quad \text{[Eq.3]}$$

Where X^+ represents the ions in the gastrointestinal tract.

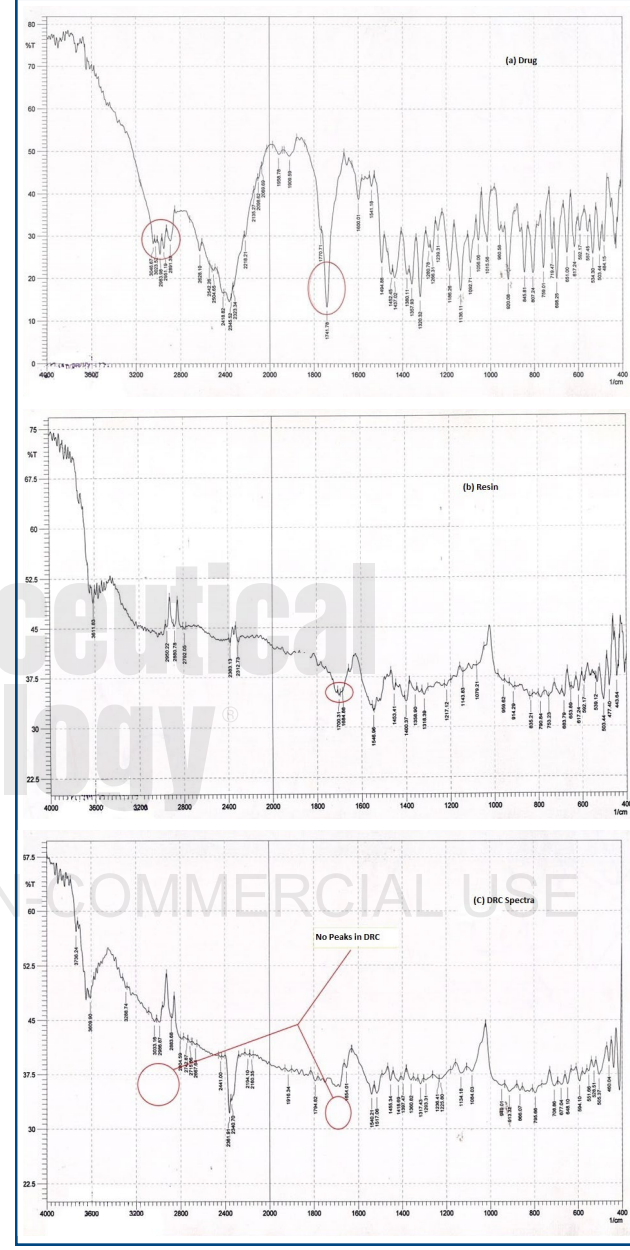
The presence of H^+ ion in the 0.1 N HCl results in the displacement of CTZ, thus facilitating drug release. The amount of drug released was insufficient to impart a bitter taste in deionized water and phosphate buffer pH 6.8.

Characterization of DRC

FTIR spectroscopy. The complexation was confirmed by IR studies. The absence of peaks at 2323 cm^{-1}–3046 cm^{-1} and at 1741 cm^{-1} in DRC denotes complexation of drug and resin. The IR spectra of complex showed that there was no observed incompatibility between drug and resin. Peaks of both drug and resin were observed and interpreted (**Figure 2**).

Reconstituted suspension. Prepared suspension was evaluated for flow properties and drug content before reconstitution. Results are shown in **Table III**. Results showed that the reconstitutable blend has excellent flow properties and optimum drug content, and that the prepared blend had good dispersion homogeneity. At the time of use, the reconstitutable blend was reconstituted with water for preparation of suspension.

Figure 2. Fourier Transform infrared spectra of (a) cetirizine dihydrochloride, (b) Kyron T-134, and (c) drug-resin complex.



Sedimentation volume of suspension. The ultimate height of the solid phase after settling depends on the concentration of solid and the particle size. In prepared formulation, there was little sedimentation after 7 days and 14 days, and the particles could be easily redispersed. Moreover, uniform dispersion was achieved after a minimum number of strokes. Results are shown in **Table IV**.

Sedimentation rate depends on the viscosity of the medium. From sedimentation volume data, it can be seen that suspension is stable and easily redispersed after 14 days. Thus, the viscosity of the suspension is sufficient to keep the suspension stable.

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The reconstitutable blend for suspension was subjected to stability studies for a period of 14 days. The samples were reconstituted in purified water to formulate a suspension. This was analyzed for pH at day 0, day 7, and day 14 after reconstitution. There was no appreciable change observed in pH and drug content. Size of the particles in suspension was reasonably constant even after 14 days. This indicated no crystal growth. Results are shown in **Table V**.

***In-vitro* drug release.** Drug release from the prepared formulation was observed in 0.1 N HCl. Results showed that nearly 85% of drug release was found from prepared suspension in duration of 5 minutes. This is happened because drug in form of DRC is weak enough to be broken down at gastric pH 1.2 and allow the rapid release of drug from suspension.

Conclusion

In the present study, an attempt was made to mask the bitter taste of CTZ by using Kyron T-134 as an ion exchange resin. Various parameters affecting taste masking, such as resin ratio, pH, temp, soaking time of resin, and stirring time were optimized with efficient loading of drug. The nature of the DRC is such that the average pH of 6.8 in saliva is not able to break the complex. *In-vitro* drug release in salivary pH of 6.8 was less than 5% within 60 s. Ideally, an oral suspension is swallowed by a patient in a fraction of that time (not more than 60 s). Yet, the DRC is weak enough to be broken down at gastric pH 1.2, thus the complex is considered absolutely tasteless in salivary fluid. Taste-masked DRC has shown excellent flow properties in this study. Furthermore, formulated CTZ reconstitutable suspension has acceptable sedimentation properties. In a 14-day evaluation period, it is observed that no significant change was observed in pH, viscosity, particle size, and drug content. This method is simple and cost effective to prepare taste-masked reconstitutable suspension of CTZ that may be acceptable to the industry.

References

1. G. Colombo, et al., "Stabilized Aqueous Suspensions for Parenteral Use," US Patent 6,495,534 (Pharmacia, Upjohn Spa, and Upjohn Co, 2002).
2. C.M. Blase and M.N. Shah, "Aqueous Pharmaceutical Suspension for Pharmaceutical Actives," US Patent 5,409,907 (Johnson and Johnson Consumer Inc., 1995).
3. K. Kuksal and K. Pathak, *Indian J. Pharm. Sci.* 70 (5) 609 (2008).
4. K. Kulshreshtha Alok, et al., *Pharmaceutical Suspensions: From Formulation Development to Manufacturing* (Springer-Verlag New York, 2010).
5. S.S. Martindale, *The Complete Drug Reference* (Pharmaceutical Press, London, 35th ed., 2007), p.515.
6. B.P. Mukherjee, *Indian J. Otolaryngol. Head Neck Surg.* 46 (3) 169–170 (1994).
7. .G. Mahore, et al., *Int. J. Pharm. Sci. Rev. Res.* 1 (2) 8–13 (2010).
8. H. Sohi, et al., *Drug Dev. Ind. Pharm.* 30 (5) 429–448 (2004).
9. J.G. Avari and M. Bhalekar, *Indian Drugs-Bombay* 41 (1) 19–23 (2004).
10. L. Santos and E.S. Ghaly, *AAPS PharmSci* 5 (S1) T3257 (2003).
11. S. Pisal, et al., *AAPS PharmSciTech* 5 (4) 84–91 (2004).
12. L. Lachman, et al., *The Theory and Practice of Industrial Pharmacy* (Varghese Publishing House, Mumbai, India, 3rd Ed., 1991), pp. 67, 183, 316–317.
13. G.A.R. Remington, *The Science and Practice of Pharmacy, Vol I* (Lippincott, Williams & Wilkins, Philadephia, PA, 20th Ed., 2002), pp.691–703.
14. V. Kharb, et al., "Bitterness Suppression of Oral Pharmaceuticals," in *The Sense of Taste* (Nova Science Publishers, New York, 2010), pp.237–276.
15. K. Mehta, "Taste Masked Microcapsules and Process for Their Preparation," Patent WO2004096175, 11.a, 2004.
16. G.C. Patel, et al., *J. Pharm. Drug Devel.* 3 (1) 1–7 (2015). **PT**

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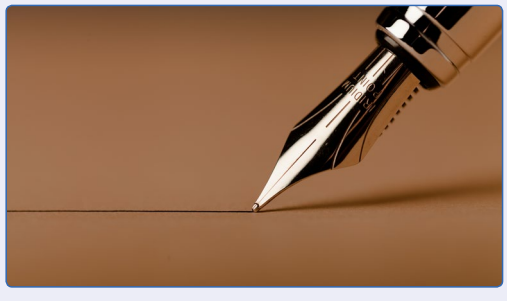

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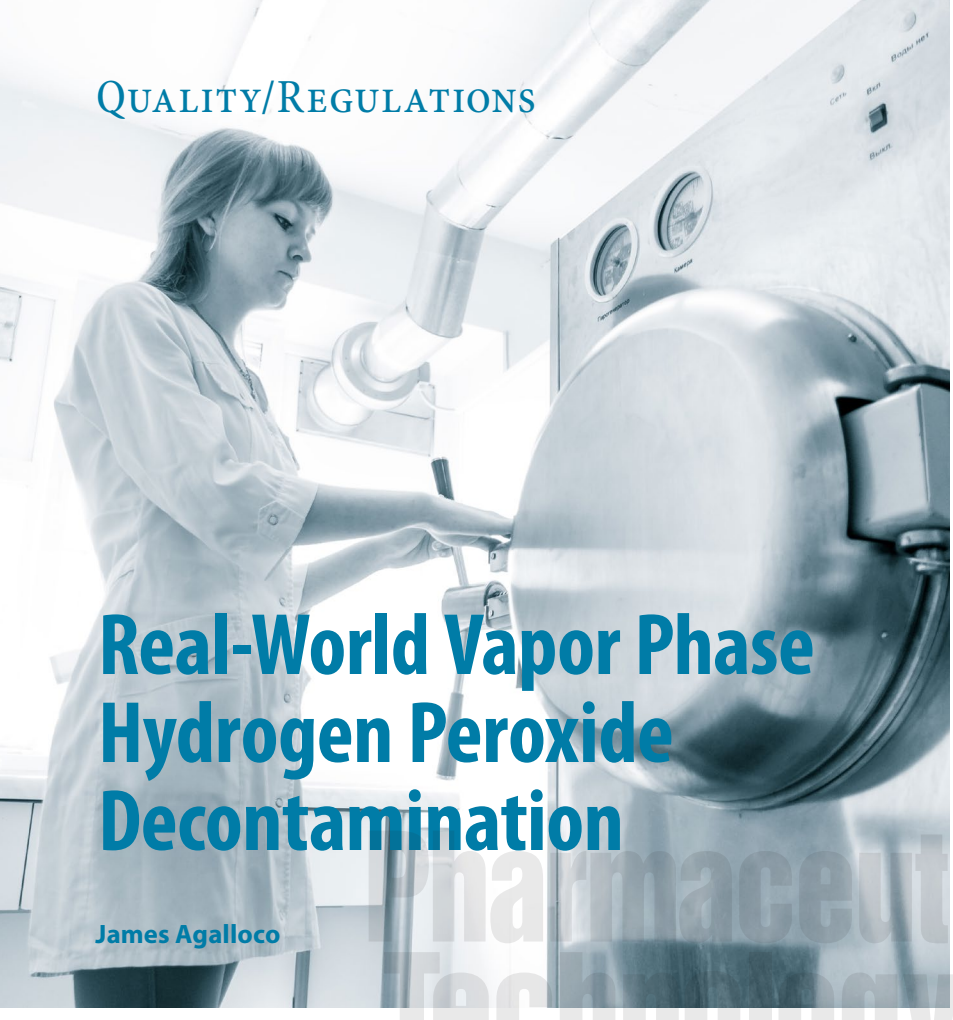

Real-World Vapor Phase Hydrogen Peroxide Decontamination

James Agalloco

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Past mistakes and misstatements have adversely influenced industry decontamination practices with vapor phase hydrogen peroxide, and this article endeavors to clarify the process.

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The introduction of isolation technology in the pharmaceutical industry by the French firm La Calhene in the 1980s required a means for the reliable microbial decontamination of the isolator interior. This was initially performed using a mist of peracetic acid/water; however, this was considered undesirable for a variety of reasons, with objections over its use primarily aimed at the resultant corrosion of surfaces, wet surfaces, and lengthy aeration times. In the late 1980s, AMSCO (now Steris) offered the first widely available alternative with their VHP-1000 generator, which delivered vapor phase hydrogen peroxide (VHP). With the introduction of the VHP-1000, this technology and its derivatives became the dominant means for isolator decontamination.

Initially, the performance expectations for the decontamination process varied according to the end user's protocol requirements. The process target (decontamination or sterilization) and the means to establish them (the biological indicator [BI] population to use and the selection of cycle duration) varied widely. Firms with near identical systems and practices considered them differently.

Regulatory influences

The first definition of process expectations was provided in *United States Pharmacopeia* (*USP*) 28 <1208>, *Sterility Testing—Validation of Isolator Systems* (2000), with an expectation for sterilization, "The sterilization methods used to treat isolators, test articles, and sterility testing supplies are capable of reproducibly yielding a six log kill against an appropriate, highly resistant biological indicator" (see **Figure 1**) (1).

The inclusion of a "six-log kill" requirement is problematic in that this terminology is uncommon in sterilization; there being no generally accepted definition for it in sterilization practice. It could be interpreted as either a six-log reduction or complete kill of a six-log population (a nine-log reduction, see **Figure 1**). Stating that and expecting "sterilization" in the first version of *USP* <1208> was clearly problematic, as sterilization is more widely accepted as a minimum 12-log reduction of a BI.

The Parenteral Drug Association issued its publication on isolators in 2001. It included several different means to establish its decontamination requirement, "for the purposes of isolator decontamination a Total Kill Analysis study of a suitable bioindicator with a population of 10^5 or greater is considered an overkill cycle. Such a cycle indicates a spore log reduction value of >7 logs" (2).

FDA formally addressed isolator decontamination first in 2002, with the initial draft of its revised aseptic processing guidance (3). The stated expectation was, "For most production applications, demonstration of a six-log reduction of the challenge BI is recommended." The draft was also explicit in stating decontamination, as opposed to sterilization, of the interior was expected. Sterilization was correctly identified as the requirement for product contact surfaces.

The European Medicines Agency, through the assembly of inspectors with the Pharmaceutical Inspection Co-Operation Scheme (PIC/S), issued its first isolator-related guidance in 2004 and aligned closely with FDA, "…, but a target of six log reductions is often applied" (4). This document was explicit in defining a six-log reduction, as not requiring the complete destruction of all microorganisms on a 10^6 population BI. This document adds confusion of a different kind by referring to the decontamination processes primarily as a gaseous process, which is a serious error (see below).

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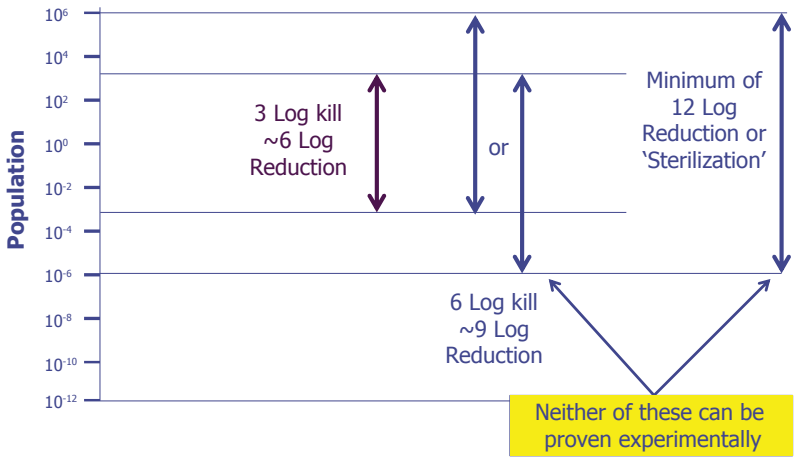
Figure 1. Log-kill and log reduction.



The final version of the FDA guidance published in September 2004 relaxed the log reduction position; "Normally, a four- to six-log reduction can be justified depending on the application" (5). This guidance in conjunction with the PIC/S six-log definition has largely shaped global industry decontamination practice to this date.

In 2008, *USP* revised chapter <1208> to align more closely with the regulatory and industry guidance documents that had been issued, "The ability of the process to reproducibly deliver a greater than three-log kill is confirmed in three consecutive validation studies" (6). In this revision, the process is now termed decontamination consistent with the other standards.

USP significantly revised its sterilization content in 2013–2018 and added vapor phase sterilization in those changes. The new content includes two related subchapters that directly impact VHP processes (7,8). The *USP* content changes expectations in many ways. First, vapors are considered two-phase systems, the presence of which substantially complicates process design and execution. Second, because of the dual-phase nature of the process, D-value estimation is not possible because the conditions of microbial death are indeterminate. Lastly, if the D-value is indeterminate, the log reduction expectations may be inadequate. The *USP*'s chapters disrupt many of the commonly held misconceptions regarding VHP validation.

A regulatory perspective was provided by the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) in an April 2018 blog on their website. "VHP, when well controlled and validated, is a useful method for the decontamination of the surrounding workspace, e.g., an isolator environment. However, given the above concerns, our current stance is that VHP cannot be used to sterilize critical items" (9). This position creates substantial difficulties for many current installations. The *in-situ* sterilization of stopper bowl, feed tracks, and many other surfaces in direct contact with sterilized items (and presumably considered "critical") is called into question by this MHRA position. Industry response has been one of alarm, as it potentially invalidates many systems current in use.

Inside the real world

A shift in perspective is essential to succeed in the changing landscape. The existing log reduction requirements are poorly suited to the emerging perspectives of decontamination using a vapor treatment. Increasing usage of vaporized hydrogen peroxide has resulted in numerous publications describing applications of various types, from small pass-through chambers to entire suites of rooms. Unfortunately, past mistakes and misstatements have been incorporated which have adversely influenced industry practices. This document endeavors to clarify the process relying on the core science underlying it. Many of the problematic statements regarding vapor decontamination are provided in this paper followed by the scientific reality.

Common misconception: Vapor phase hydrogen peroxide decontamination is a single phase gas process.

Scientific reality: There are varying definitions of vapor, some of which suggest that vapors are equivalent to single phase gas mixtures. However, at the ambient temperatures used for VHP processes condensation of hydrogen peroxide (H_2O_2), and, to a lesser extent, water (H_2O), is unavoidable (10,11). Vapor decontamination processes operate below the boiling point of both materials, and, while some of each will remain in the gas phase due to their vapor pressure, they are both liquids at ambient temperature. The amount of H_2O_2 and H_2O maintained in the gas phase decreases as the temperature decreases below that used to introduce them into the system. Thus, VHP must be understood to be a two-phase process in which both gas and liquid are present. Depending on the amount of liquid phase present, it may or may not be visible. The original characterization of VHP as a completely gas phase process originates in the originating patent; however, the inventors did not consider or determine what phase was actually present at the point of kill (12).

Common misconception: The kill of resistant BIs by H_2O_2 is more rapid in the gas phase than in the liquid phase.

Scientific reality: The experiments that support this claim can be interpreted differently to assert that the exact opposite is true (13). No determination of phase or concentration measurement at the point of kill was performed in the experiments. Condensation is highest at the lowest operating temperature, and these demonstrated the fastest kill rate. Published data on H_2O_2 solutions indicate that spores are killed extremely rapidly (14–16). This suggests that liquid-phase kill will be more rapid than gas-phase kill because the concentration of H_2O_2 in the liquid will always be higher than in the gas phase (17). This

FIGURE COURTESY OF THE AUTHOR.

has been independently confirmed in challenge studies conducted using various decontamination systems (18–20).

Common misconception: VHP decontamination is a single phase gas process that resembles ethylene oxide (EtO) and other sterilizing gas processes.

Scientific reality: Considering gases and vapors as identical goes to the very origins of hydrogen peroxide decontamination (12,21). The confusion in terminology may originate in the means to introduce a 35% aqueous solution into a hot air stream where high heat rapidly converts the H_2O_2 aqueous solution into a multi-component gas at elevated temperature. Above their boiling points, both liquids are converted to gases. The hot gas mixture is introduced into the ambient temperature target system where it loses heat to its surrounding surfaces. As this occurs, the H_2O_2 and H_2O concentrations in the gas phase are above their saturation vapor pressure and condensation must occur (22). The presence of two phases in an ambient-temperature vapor hydrogen peroxide process is unavoidable. Hydrogen peroxide having a higher boiling point and lower vapor pressure than water condenses first and concentrations of H_2O_2 in the liquid phase will be higher than the original solution percentage.

Common misconception: Because VHP decontamination is a gas phase process, temperature is not an important influence on process lethality.

Scientific reality: VHP is a multi-phase process with both liquid and gas phases present (23). The amount of condensation on the surface is directly related to the local temperature. As the H_2O_2/H_2O solution is first vaporized and then introduced with hot air, there will be temperature differences across the system. The hottest areas, typically closest to the vapor inlet and any operating equipment, are potentially "worst case" because of reduced condensation. Changes in temperature during the process duration are somewhat unavoidable, especially in smaller chambers, which will alter the amount of condensation and, thus, process lethality. It is important to maintain near-constant room conditions to minimize process variability during the individual VHP process and between multiple VHP cycles over time.

Common misconception: Measurement of H_2O_2 gas concentration can be used to reliably control VHP processes.

Scientific reality: The gas- and liquid-phase concentrations at any location is dependent upon the temperature of the system at that location. Gas-phase measurement cannot be used to estimate concentrations on the surface unless the system reaches equilibrium. Variations in temperature across location and process duration are unavoidable with most VHP processes, which minimizes the utility of concentration measurements taken in the gas phase.

Common misconception: Condensation during VHP decontamination is to be avoided, as it slows kill and extends aeration times. Thus, dehumidification prior to processing helps prevent condensation.

Scientific reality: Condensation is unavoidable, and, while not always visible, it actually supports more rapid kill (see previous scientific explanations), condensation being necessary to assure rapid kill is actually desirable. Dehumidification prior to the introduction of H_2O_2 is unnecessary because it delays condensation, thus, increasing process time and system cost. Kill is quicker in condensing systems such that the process dwell can be shortened substantially.

Common misconception: Condensed H_2O_2 on surfaces is a corrosion and explosion hazard and is to be avoided.

Scientfic reality: Corrosion is not a concern when appropriate materials are used for construction of the system. Condensation of H_2O_2 has always been present, even if not always readily visible. Nevertheless, in more than 30 years of vapor phase hydrogen peroxide use, there has never been a reported explosion. This includes the many newer systems where H_2O_2 is intentionally condensed to expedite the process.

Common misconception: Condensation of H_2O_2 on surfaces can result in greater adsorption of H_2O_2 than a gas phase process without condensation. This can result in lengthy aeration.

Scientific reality: Gases can permeate Tyvek wrapping and be readily absorbed by polymers, while condensed liquids cannot permeate the hydrophobic material and remain on the exterior surface. It might seem counter intuitive, but a "wet" process can result in less adsorption than a "dry" process. Note that the distinction between "wet" and "dry" processes is an artificial one. As mentioned, all VHP processes have some condensation present, so the "wet" vs. "dry" distinction refers to the differing beliefs of whether kill occurs best when the BI is contacted with a liquid or a gas. With rapid kill, diffusive adsorption of H_2O_2 from the gas phase is reduced and overall process duration may be shorter in "wet" processes than in "dry" processes. The longest segment of many VHP cycles can be the aeration period, which is limited by slow desorption of H_2O_2 from polymeric materials and permeable packaging.

Common misconception: Labeled "D-values" for VHP BIs are definitive and accurate (author's note: throughout the document, the term "D-values" in quotes denotes instances where it is believed that the values are improperly identified as such, and the term D-values without quotes is used elsewhere).

Scientific reality: A D-value can only be established when the conditions (concentration, relative humidity, and temperature) to which the microorganisms are exposed are known (8). The presence of two phases in VHP systems makes D-value determination impossible. BIs labeled for VHP processes do not state the conditions of kill, but typically cite the H_2O_2 injection rate in the BI manufacturers test system. The injection rate cannot be correlated to precise and reproducible destruction of microorganisms in a different system. None of the BI labels report accurate "D-values" because the conditions at the point of kill are unknown and, thus, the labels themselves are misleading.

Common misconception: Vendors selling VHP BIs provide reliable "D-values" on their certificates of analysis.

Scientific reality: BI vendors have responded to customer expectations and the "D-value" information they provide does assure consistent resistance for their products, but only in the BI vendors test system (24,25). The performance of those same indicators in users' systems cannot be predicted from the certificates pro-

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vided because of the differing conditions in the users' systems.

Common misconception: Publications showing the effect of varying materials on the "D-values" of BIs in VHP processes are useful because the BIs used in those studies are positioned on the surface (26–29).

Scientific reality: As stated earlier, D-value can only be established when the conditions (concentration, relative humidity, and temperature) to which the microorganisms are exposed are known (8). The various studies do not provide that information, however. Further, because the internal conditions inside the various systems must be understood to vary with location and time, the relative resistance associated with different materials and finishes cannot be established.

Common misconception: BIs for VHP can demonstrate anomalous behavior (30,31). These are often termed "rogues", and their survival is an indication of defective BIs, not flaws in the process being evaluated.

Scientific reality: BIs are produced for a variety of sterilization processes using well-established and consistent methods. There is no comparable problem with "rogue" BIs associated with any sterilization or decontamination process other than VHP. The "rogue" BI is more likely the result of poorly defined decontamination processes where the lethality delivered is insufficient to kill all of the BI microorganisms present.

Common misconception: Because there are "rogue" BIs, multiple BIs should be used with all VHP decontamination processes.

Scientific reality: Properly developed VHP processes that use sufficient H_2O_2 to create modest amounts of condensation have been proven reliable without resorting to multiple BIs in an attempt to compensate for either a minimally lethal or excessively variable decontamination process.

Common misconception: A "system D-value" can be used to establish reliable VHP processes; "D-value of a BI measured in a specified gas generator/separative enclosure combined with a defined sporicidal vapor-phase (decontamination cycle)" (31).

Scientific reality: As indicated previously, D-value determination requires maintenance of specified conditions (concentration, relative humidity, and temperature). This is not currently possible for two-phase systems using a BIER type design (5,8). Suggestions that it could be achievable and useful in the operation of a large system with potentially greater variation in the critical parameters are poorly founded.

Summary recommendations

Putting aside the unusual MHRA blog position, there are principles and practices to follow with respect to VHP decontamination that include:

- The BI should have a population of 10^4 colony-forming unit (CFU)/unit where decontamination is the process expectation.
- BI positioned on product contact surfaces should have a population of 10^6 CFU/unit where sterilization must be demonstrated.
- All BIs should be fully inactivated. The use of multiple indicators at each location is unnecessary, especially if the intent of multiple BIs is to explain away positive results.
- VHP is most effective when provided using a "wet" process, and this may entail the use of greater quantities of H_2O_2.
- Labeled "D-values" for VHP processes are inaccurate and should never be used to determine cycle duration. They may be useful in comparing different BI lots from the same manufacturer.
- Log-kill times cannot be estimated from "D-values" and can only be established using BIs in the system being evaluated.

Conclusion

The preceding could be misinterpreted as denigrating the utility and efficacy of VHP as a decontaminating or sterilizing agent. There are certainly difficulties with its use; however, properly delivered, its many advantages outweigh the negative aspects and assure its continued and expanded usage (22). It lacks the simplicity of a gas process, and adaptation to the unique requirements of its two-phase nature is essential to success. Reliable decontamination/sterilization cycles and systems require the following:

- Acknowledgement that condensation is a necessary element of reliable kill
- Awareness that BIs provide prima facie evidence of lethality
- Abandonment of gas concentration as a useable metric
- Acceptance of empirical evidence based on BI destruction as the definitive indicator of process suitability.

In spite of it being misrepresented as a single-phase gas process, hydrogen peroxide usage has increased steadily since its introduction. The cited difficulties have been overcome by many practitioners. Implementing vapor H_2O_2 processes following sound scientific principles of chemistry, physics, and engineering can establish designs for the delivery of a complex, but lethal, chemical agent in the most effective manner. Numerous vendors and end users have realized success with vapor hydrogen peroxide, and, despite the difficulties, some have experienced, increased future use is near certain.

References

1. USP, <1208>, "Sterility Testing—Validation of Isolator Systems" *USP 28* (US Pharmacopeial Convention, Rockville, MD, 2000).
2. PDA, *TR 34: Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products* (Bethesda, MD, 2001).
3. FDA, *Draft Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing, September* (Rockville, MD, 2002).
4. Pharmaceutical Inspection Co-Operation Scheme, *Recommendation on Isolators Used for Aseptic Processing and Sterility Testing*, PI-014-2, July 2004.
5. FDA, *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing* (Rockville, MD, September 2004).
6. USP, <1208>, "Sterility Testing—Validation of Isolator Systems" *USP 30* (US Pharmacopeial Convention, Rockville, MD, 2008).
7. USP, Supplement 1, <1229.11>, "Vapor Phase Sterilization" *USP 38* (US Pharmacopeial Convention, Rockville, MD, 2015).

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8. USP, Supplement 1, <1229.5>, "Biological Indicators for Sterilization" *USP 39* (US Pharmacopeial Convention, Rockville, MD, 2016).
9. MHRA, "VHP (Vapour Hydrogen Peroxide) Fragility," *MHRAInspectorate.blog.gov.uk*, April 20, 2018, https://mhrainspectorate.blog.gov.uk/2018/04/20/vhp-vapour-hydrogen-peroxide-fragility/.
10. W.M. Haynes, Ed., *CRC Handbook of Chemistry and Physics* (CRC Press LLC, Boca Raton, FL, 95th ed., 2014) pp. 4–67.
11. T.E. Daubert, and R.P. Danner, *Physical and Thermodynamic Properties of Pure Chemicals Data Compilation* (Taylor and Francis, Washington, DC, 1989).
12. USPTO, "Hydrogen Peroxide Vapor Sterilization Method," US Patent 4,169,123, Sept. 25, 1979.
13. D. Eddington, et al, "Chemical and Biological Aspects of Hydrogen Peroxide Vapor," Presentation at ISPE Barrier Isolation Technology Conference (Washington, DC, 2000).
14. R. Toledo, et al., *Applied Microbiology*, 26 (4) 592–597 (1973).
15. S.S. Block, "Peroxygen Compounds," in *Disinfection, Sterilization and Preservation* (Lippincott Williams and Wilkins, Philadelphia, PA, 5th ed., 2001), pp. 185–204.
16. M. Ahlgren, and Z. Bjorkland, "Robustness of a Biological Indicator Resistance Test Rig—a Study of Different Parameters, Methodologies, and Their Impact on the Measured D-value of the Biological Indicator," Lund University, LTH School of Engineering, 2005.
17. C. Hultman, et al., *Pharmaceutical Engineering* 27, 22–32 (2007).
18. J.E. Akers, et al., "A New Approach to VPHP Decontamination," presentation to ISPE, 2006.
19. D. Watling, "Is H_2O_2 a wet or dry process?" presentation at PDA Isolator Technology Conference, April 29-30, 2002.
20. B. Unger-Bimczok, et al., *J. Pharm. Innovation* 3, 123–133 (2008).
21. G.S. Graham, et al., "Sterilization of Isolators and Lyophilizers with Hydrogen Peroxide in the Vapor Phase," proceedings from the International Congress of the Parenteral Drug Association (Basel, Switzerland, 1992), pp. 32–51.
22. J. Agalloco and J. Akers, *Pharmaceutical Technology* 37 (9) 46-56 (2013).
23. D. Watling and M. Parks, *Pharmaceutical Technology Europe*, 16 (3) (2004).
24. G. Krushefski, *Spore News* 9 (4) (2009).
25. J. Drinkwater, et al., *EJPPS* 14(1) 5–11 (2009).
26. V. Sigwarth and C. Moirandat, *PDA J Pharm Sci Technol* 54 (4) 286–304 (2000).
27. V. Sigwarth and A. Stark, *PDA J Pharm Sci Technol* 57 (1) 3–11 (2003).
28. T. Mau, et al., PDA J Pharm Sci Technol 58 (3) 130–146 (2004).
29. B. Unger, et al., *PDA J Pharm Sci Technol* 61 (4) 255–275 (2007).
30. P. Templeton and J. Hillebrand, "Case Study: Isolator Sanitisation Cycle Development, Validation and Revalidation," presentation at ISPE Isolation Barrier Forums (Washington, DC, and Prague, 2005).
31. PDA, *TR 51: Biological Indicators for Gas and Vapor-Phase Decontamination Processes: Specification, Manufacture, Control and Use* (Bethesda, MD, 2010). **PT**

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A Q&A

Single-Use System Integrity

Marc Hogreve
Principle Engineer for Integrity Testing
Sartorius Stedim Biotech

An integrity-assurance strategy for single-use systems can mitigate risks and uphold regulatory compliance in biopharmaceutical manufacturing.

As adoption of single-use systems in more critical process steps of biomanufacturing increases, strategically maintaining and protecting the integrity of such systems is paramount to producing safe and efficient biologic drugs.

BioPharm International and *Pharmaceutical Technology* recently sat down with Marc Hogreve, Principal Engineer for Integrity Testing at Sartorius Stedim Biotech, to discuss the company's integrity-assurance strategy for single-use systems.

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BioPharm/PharmTech: Why is single-use system integrity a hot topic in the industry?

Hogreve: Classical, container-closure integrity for primary packaging containing final drug product has been an important topic in the past. But why should it be different for single-use systems used in the manufacturing of these drugs?

As single-use systems are increasingly being used in all process steps of commercial manufacturing, integrity failure can have a significant impact on drug safety, availability, and costs. As a consequence, growing industry scrutiny of single-use system integrity increases the need to develop good science behind the detection of liquid leakage and microbial ingress mechanisms, and to use appropriate physical integrity-testing technologies. Sartorius Stedim Biotech developed this pioneering science and technology for higher integrity assurance.

BioPharm/PharmTech: How is Sartorius addressing this demand?

Hogreve: Sartorius has compiled a strong integrity-assurance strategy that has three pillars: consistent robustness, integrity science, and integrity-testing technologies. Consistent robustness is the basis for strong integrity assurance for single-use systems. Because testing quality into non-robust products is not an appropriate approach, it is best if quality is consistent right from the start.

Nevertheless, integrity testing is part of Sartorius' strategy. To develop appropriate integrity-testing technologies, it is critical to understand integrity science—the failure modes, defect characteristics, and barrier properties related to the integrity of the company's single-use systems.

Last but not least, Sartorius has developed several integrity- and leak-testing technologies to confirm the system integrity of its products, both in manufacturing as well as at the customer site.

BioPharm/PharmTech: You mentioned that consistent robustness is the basis for integrity assurance. What exactly do you mean by that?

Hogreve: As I mentioned, it does not make sense to test quality into non-robust products. Robustness becomes a critical quality attribute of a single-use system when a product range is developed according to quality-by-design principles. The final product robustness is the result

of several ways of measuring quality, which cover the entire production chain—from testing resin properties and inspecting the films and bag chambers manufactured, to monitoring welding and assembly processes.

In addition, Sartorius performs the most stringent liquid-shipping validation in accordance with ASTM D4169 to confirm the robustness of its products under real-use and laboratory conditions. Records of this validation show that Sartorius' Flexsafe® bags can withstand acceleration forces up to 20 g.

BioPharm/PharmTech: How can integrity science help to enhance the integrity of single-use systems?

Hogreve: Mitigating risks as part of a quality risk-management approach has become a key requirement imposed by the pharmaceutical industry and regulatory authorities. Most recently, it has led to the revision of Annex 1, "Manufacture of Sterile Medicinal Products."

As a result of companies' quality risk-management plans for improving process integrity, it may be required to implement an integrity-testing strategy to meet regulatory expectations and increase patient safety. This is possible only if liquid leak and microbial ingress mechanisms are thoroughly understood so that the levels of detection can be determined, which are the maximum allowable leakage limits, or MALLs. Physical integrity test methods must detect MALLs to correlate such levels of detection to leak sizes causing liquid loss and microbial ingress.

BioPharm/PharmTech: Is determination of the MALL required to implement meaningful integrity testing? How exactly is this determination made?

Hogreve: Common applications such as storage and shipping are performed under process conditions that may have an impact on the leak size, causing liquid leaks and microbial ingress. Considering storage conditions, static pressure affects the leak size. Take the example of a 500-L bag or a suspended 20-L bag with a column water height of approximately 0.7 m, which corresponds to a hydrostatic pressure of 70 mbar.

Regarding shipping conditions, the differential pressure during shipping has no impact on a flexible container, unlike on a vial. Instead, the impact results from the acceleration and/or shocks that such a bag will experience during shipping. This will affect the leak size and can be considered worst-case process conditions.

In total, four different test pressures and three different model solutions were selected to establish a theoretical model that can be used to predict the MALL under any process condition. With these parameters, a significantly large number of tests on several hundred samples have been (and are still being) performed to characterize the liquid leak and microbial ingress mechanisms on the company's film materials. For both studies, film patches with laser-drilled holes of various leak sizes are used. Liquid leak samples are pressurized for up to 30 days under continuous visual inspection to detect any liquid leaks using indicator paper.

> "As a result of companies' quality risk-management plans for improving process integrity, it may be required to implement an integrity-testing strategy to meet regulatory expectations and increase patient safety."

Microbial ingress samples are challenged by aerosolization for three hours, with a challenge concentration of 10^6 CFU/cm^2 *Bacillus atrophaeus*, subsequently incubated for two weeks and then visually inspected for growth. With this testing, Sartorius is able to define the MALLs for its products and consequently use them as detection limits for the company's physical integrity testing technologies.

BioPharm/PharmTech: Can you give us an overview of these physical integrity testing technologies?

Hogreve: Sartorius is the only company that has been able to identify the MALL under process conditions and develop a technology capable of detecting the defect size that correlates to microbial ingress. Sartorius' in-house helium integrity tester provides a sensitivity of 2 µm, and its pressure decay point-of-use integrity test method 10 µm, so both of these values correlate to the MALL determined under process conditions in which the company's 2D and 3D bags are used.

In addition, Sartorius provides a huge variety of point-of-use leak testing across its product portfolio. This is mainly done post installation into the final container to cover all potential gross leaks that may have been introduced during shipping, handling, and installation of the single-use system. With this, customers can confirm the system integrity right before use.

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Getting to the Root of Quality Problems

Agnes Shanley

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Focusing on symptoms instead of root causes locks manufacturing and quality teams into a corrective, rather than preventive, mindset.

The philosopher George Santayana once wrote, "Those who fail to learn from the past are condemned to repeat it." This is clearly seen in the way that some pharmaceutical manufacturers approach root cause analysis (RCA) and corrective action and preventive action (CAPA).

Both RCA and CAPA are closely intertwined. For example, tracking and trending complaints allows companies to identify recurring problems that may not be caught during inspections on the manufacturing floor, says Kim Jackson, product manager at MasterControl, a vendor of quality management and CAPA software. It also allows them to determine the true severity of specific problems or failure modes, she says. Furthermore, CAPA effectiveness checks ensure that RCA investigations are sufficiently robust, says pharma quality consultant Ajay Pazhayattil. Both concepts are crucial for establishing continuous improvement and a true culture of quality, and achieving the goals established by International Council for Harmonization (ICH) Q 12. "Efforts always pay off because they prevent supply disruptions and resulting revenue loss," says Pazhayattil. Addressing them incorrectly, however, can lead to product quality failures as well as noncompliance with current good manufacturing practices (CGMPs). Between October 2018 and November 2019, FDA issued 81 warning letters (the highest number seen in five years) to finished pharmaceutical manufacturers for CGMP deficiencies, with more than half of them sent to companies in the United States, according to the European Compliance Academy. Nearly half of these citations found that quality control departments had not been set up or staffed properly, and that their responsibilities were not clearly defined (1).

In some cases, particularly for over-the-counter (OTC) drugs, the problems highlighted in warning letters had already been pointed out previously in FDA Form 483s, suggesting a need for more senior management involvement and greater investment in CGMP compliance. Inspectors pointed to inadequate validation and conformance to written procedures, as well as deficient RCA and CAPA. In some cases, root causes for batch or product testing failures were either insufficiently investigated or not probed at all (2,3).

Experts see a number of reasons for this situation, including the need for a more rigorous approach to risk assessment and a better understanding of the cost of poor quality. "If we as an industry could step up and own the cost of poor quality, if we could measure it, we'd be horrified at what we pay, not just for failing to solve issues but for repeatedly solving the same ones," says Nuala Calnan, principal of the consulting firm BioPharm Excel and professor at the Technical University of Dublin. "The number of person-hours and CAPAs that arise from these investigations is eyewatering. We don't add them all up and have a number that we can track (i.e., 'that's how much it cost us not to get to root cause and to keep on failing')," she says.

But there has also been a lack of good RCA training at many pharmaceutical manufacturers. In October 2019, the International Society for Pharmaceutical Engineers (ISPE) and the Parenteral Drug Association (PDA) launched their joint Quality Culture guidance series with a module devoted to best practices for RCA (4), in an attempt to address this problem. Its goal is to help shift the industry's focus from compliance to prevention. "Pharma companies typically cover fundamentals (e.g., how to use tools such as Five Why's and Ishikawa fishbone diagrams), but teaching people how to use tools and templates isn't training them to look

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at the underlying science behind RCA decision making and why it is so important," says Calnan, who is also co-leader of ISPE's quality culture initiative and one of the authors of the new RCA module.

Advanced training in the techniques and critical thinking required for investigators, and application of proven RCA tools such as mapping, brainstorming, cause-and-effect, and Five Whys are crucial to improving the state of RCA in the industry, says Pazhayattil. "It's important not to get stuck on using the same methodology each time, since different problems will call for different solutions," suggests Marzena Ingram, a senior pharma quality manager who comments as an industry professional rather than on behalf of her company.

Feeding the compliance beast

Impeding a better approach to RCA at many companies is an ingrained focus on regulatory compliance and being inspection-ready. "Many quality departments must focus on feeding the compliance system rather than considering quality as a broader responsibility. Often, we're being driven to close out investigations within 30 days because compliance metrics tell us we need to do that, so we're not addressing root cause," says Calnan.

In some cases, companies may overrespond to smaller quality problems by launching too many full-scale RCA investigations, says Jackson. "When a company goes into full alert, all-hands-on-deck mode for every issue that arises, not only does time get wasted, but employees become jaded and less likely to do due diligence when a real issue presents itself," she says. "Taking a risk-based approach to escalations and root cause investigations saves efforts for issues that truly pose a risk to patient health and safety," she says. Jackson suggests that each quality event be investigated first at a lower level to determine the most likely cause, and then evaluated for risk.

Another fatal flaw in many RCA programs is that the approaches typically address only part of the problem, its symptoms, or its direct cause, rather than the fundamental reason why it happened. For example, operator error, which is often cited as the reason for quality problems, usually shows that the system of controls in place for the process and product has failed, rather than any single individual staff member, Calnan says.

In other cases, the reason behind the direct cause for one batch's failure (e.g., a product or labeling mix-up) may be solved without considering the series of events that caused the mix-up to occur in the first place. In all these cases, companies wind up cutting and pasting the same solutions to each new problem, whether or not they have worked in the past. "Because the root cause hasn't been addressed, the problems will recur," Calnan says.

Success with RCA requires rooting out any potential sources of bias, says Pazhayattil. "It is human nature to pre-empt causes of failures, but theoretical assumptions should never bias an investigator," he says. For example, an investigator may unconsciously or consciously focus on the area that he or she is more familiar with (e.g., process engineering or analytical methods). "Generating sound supporting proof is critical to confirming root causes and developing a science- and data-driven investigation method," he says.

"Coming into an investigation with a biased opinion, even if you are fairly sure you're right, is a surefire way to miss the opportunity to investigate with an open mind," says Ingram. "No ideas are bad ideas, so it's best for teams to brainstorm, throw all possibilities up on the board and then rule out, systematically and with proper justification," she says.

Diversity of opinion needed

Calnan also sees an overemphasis on consensus-building as impeding the effectiveness of pharma risk management and RCA. With group efforts such as failure modes and effects analysis (FMEA), which require teams to agree on a numerical value to assign to each specific risk, there may be a failure to invite diversity of opinion or different perspectives.

Devil's advocates needed

"Consensus [can become] the enemy of good critical thinking and risk management," she says. When teams are analyzing a quality problem, Calnan suggests that one or more members play devil's advocate and ask for data or other evidence to support any hypotheses. "In some cases, companies may be pushing for agreement way too soon, before they've spent enough time or applied any real rigor to identifying the real issues causing the problem," she says.

"There is very little in pharma's processes that gets us back out there, onto the lab or manufacturing floor, to shake down the cursory one liner that was given as the reason for the problem. As a result, companies often solve for the wrong problem. When they haven't even identified the right problem, how can they get to its root cause?" Calnan asks.

Learning from failure and trending

Another obstacle to improvement is the fact that the industry doesn't typically view failures as an opportunity for learning, says Calnan. "All too often, we have to classify failures, include them in an investigation report, and apply a CAPA to them to move them off our desks so that we can get to the next round of firefighting," she says. Trending should be done regularly, as suggested by FDA's revised process validation guidance, to find where sources of variation and potential risk and failure are developing, she says, adding that "we need to see what trends are saying, using systems-based and group-theory thinking." Market complaints, stability data trends, and multivariate analysis of critical process parameters and critical quality attributes are all sources of data for continuous quality improvement says Pazhayattil.

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In addition to evaluating risk for individual events, monitoring should be put in place to help identify recurring trends that should be investigated, says Richards. If an issue is recurring, or multiple events point to the same recurring cause, the recurrence can be investigated, and a risk assessment performed on the trend. Based on that, a company could continue to monitor, setting a threshold of acceptance, or initiate a full RCA and CAPA, she says. When a full root cause investigation is warranted, having a standard methodology can help streamline the analysis, she says. For example, the use of Five Whys provides structure to the investigation and can help contain its scope while ensuring thoroughness.

Staffing and training issues

Staffing cross-functional teams offers an opportunity to ensure that the right skill sets are available for RCA. "I am seeing more such teams in action today, but many of them still take an 'us vs. them' approach," says Calnan. This often comes out most clearly in the interpretation of such phrases as 'the quality department is responsible for closing out the investigation.' While not meant as an excuse to pass the buck, this phrase often results in quality executives having to develop solutions without enough input and insight from the team, including insights from those much closer to the problem," says Calnan.

"The belief that the responsibility to assess and address root cause is 'someone else's problem' is a typical pitfall in pharma RCA programs," says Ingram. "All departments, even those that may not have direct involvement, should play a role in identifying, analyzing and effectively solving the problem and measuring the effectiveness of any changes employed," she says.

Training and knowledge management can also be an obstacle in some companies, where subject matter experts (SMEs) are almost empowered not to share knowledge. "SMEs need to see themselves as knowledge stewards and trainers for the next generation, and essential to creating a learning organization," says Calnan.

Teams may be pushing for consensus before they've been able to pinpoint the real issues causing quality problems.

Beyond training and procedures, pharma's quality metrics themselves must change if the industry's RCA and quality programs are to improve, Calnan says. She points to a need for leading (rather than lagging) metrics that are aligned with overall patient and business priorities. One example, she says, would be measuring the ratio of preventive actions to corrective actions within CAPA systems, and setting a target to move performance to the next higher level.

Accounting for recurring deviations

In addition, Calnan says, recurring deviations need to be correctly coded and accounted for. Currently, most companies don't code errors in a transparent way that would make it easy to see when they recur. "They're looking for the exact same error to happen on the exact same line or process, rather than asking whether there are common root causes and coding those causes appropriately," she says.

For example, an organization can have one problem in a lab and another on the manufacturing floor that may seem very different yet share the same root causes. "If we were being meaningful about counting recurrent deviations and driving that number down not by not counting them but by preventing them, performance would improve," says Calnan.

A potential role for emerging technologies

A number of technologies are available that promise to improve the way pharma handles RCA and to make the process easier. More powerful data analytics approaches are already being used to allow data to be drawn from disparate databases to be used for risk analysis and RCA, says Calnan. "Technology can also be leveraged to gather failure modes and occurrence data to better inform risk assessments, preventing unnecessary RCA activities when a simple mitigation would suffice," says Jackson.

Machine learning and artificial intelligence (AI) tools (e.g., predictive modeling for equipment maintenance, manufacturing process control, and real-time release) are also emerging, says Pazhayattil, who is currently working on research into AI in pharmaceutical manufacturing with CalSouthern. However, it will be a long time before these technologies are found on every floor, says Calnan.

Modern equipment, such as sterile fill and finish systems that use automation and isolators, can help improve overall operations. However, Calnan says that investing in advanced equipment is not essential to preventing quality failures.

Doing RCA correctly needn't be expensive, she says. "As an industry, we need to get on with real training. People need to understand the science behind failure, and to understand the differences as well as the connections between risk and failure," she says.

References

1. ECA GMP, "A Look at FDA's Warning Letters Over the Last Months," *gmpcompliance.org*, Nov. 1, 2019.
2. FDA, "FDA Warning Letter to Torrent Pharmaceuticals," *fda.gov*, Oct. 8, 2019.
3. FDA, "FDA Warning Letter to Lupin Ltd.," *fda.gov*, Sept. 10, 2019.
4. ISPE, "ISPE and PDA Guide to Improving Quality Culture, Module 1: Root Cause Analysis," *ispe.org*, Oct. 7, 2019.

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Prioritizing Sustainable Packaging

Hallie Forcinio

Pharmaceutical companies work toward a circular economy.

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Concerned about waste, plastic pollution of the oceans, and resource depletion, consumers want packaging materials that are minimal yet protective, renewable, recyclable, reusable, and/or contain recycled content, with clear instructions for package recycling. To earn an eco-friendly reputation, packaging must be designed with sustainability in mind, which requires paying attention to all components, including inks and adhesives, as well as disposal scenarios. Many pharmaceutical companies, retailers, and other members of the pharmaceutical supply chain have set sustainability goals and are ramping up efforts to reduce waste in support of a circular economy.

AstraZeneca, for example, has several sustainable packaging initiatives underway, including the launch of a blister laminate that reduces waste, a mail-back pilot program to collect used inhalers, and efforts to prevent pharmaceuticals from contaminating the environment (1).

Bristol-Myers Squibb (BMS) is working to meet a 2020 deadline for its current set of sustainability goals. Waste management is one focus. As a result, the company is conducting a software-based lifecycle analysis to assess the environmental impact of packaging materials used for certain products (2). The company also has eliminated polyvinyl chloride (PVC) bottles and trays and has reduced the use of PVC in blister packaging with the goal of eventually eliminating it entirely (3).

Other efforts include simplifying a packaging insert in accordance with recommendations in the company's *Sustainable Packaging Design Guideline*. This change saved 70 tons of paper per year and allowed more product per pallet, which reduced ocean container requirements by 30%. The result? Resource conservation, waste reduction, lower greenhouse gas emissions, and a savings of more than $2 million annually (3).

For BMS's Orencia (abatacept), a *Household Generated Sharps Management Plan* offers guidance, instructions, and/or recommendations for handling and proper disposal of sharps. Users of the self-injected product also may participate in a no-cost, mail-back program (4).

At Merck (known as MSD outside the US), *Design for Environment* guidelines help engineers minimize package sizes and specify more environmentally friendly materials. In 2018, a packaging design change for some of its solid-dose products increased the number of doses per case and reduced the weight of the packaging by approximately 25%. The reduction in materials lowered transportation requirements and greenhouse gas emissions (5).

Promoting the circular economy

To support the movement toward a circular economy, several groups have developed guidelines for more sustainable packaging. A *Recycling Playbook* developed by Walmart in collaboration with Pure Strategies, The Association of Plastic Recyclers, and the Sustainable Packaging Coalition, helps suppliers pursue recyclable packaging and recycled-content goals (6). It discusses what type of plastic packaging is more easily recyclable, identifies recycling challenges for certain packaging materials, and supplements the Walmart sustainable packaging playbook, which describes best practices such as optimizing packaging design and using consumer-friendly recycling labels (7).

Greener packaging options

With high interest in renewable content, recycled content, and source reduction, packaging suppliers are introducing more environmentally friendly products. A collaborative effort by jARDEN Plastic Solutions, SACMI Group, and Milliken has developed a lightweight high-density polyethylene (HDPE) pharmaceutical bottle. The design de-

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Figure 1. Tubes can be designed for recyclability.

pends on a barrier additive from Milliken and proprietary compression blow forming equipment from SACMI, which are used by jARDEN Plastic Solutions to produce thin-wall bottles that are up to 28% lighter than standard designs. The strong, lightweight containers offer excellent barrier performance, require less energy to manufacture, and generate less scrap (8).

To improve the recyclability of tube packaging, Hoffmann Neopac has published the *Tube Design Guide for Recyclability*. As shown in **Figure 1**, it recommends a thin-walled body and shoulder consisting of PE or polypropylene (PP) with less than 5% barrier content, lightweight caps of the same material as the tube body, natural or light coloring, and minimalist graphics with solvent-free, ultraviolet-cured inks and varnish. "Sustainability and recyclability can be particularly challenging in the pharma sector, where packaging solutions must protect and preserve the efficacy of important medicines and complex formulations," said Martina Christiansen, head of Pharma sales and marketing at Hoffmann Neopac. "We see this guide—and the tubes that can be produced by adhering to it—as an important step in an ongoing process to make pharma packaging more eco-conscious." The company also offers an EcoDesign portfolio that includes the Recycled Tube, featuring 75% recycled, food-grade compliant PE; Sugarcane Tube, made from renewable raw materials and offering the same characteristics and processability as fossil-based PE; and PICEA Tube, comprised of 95% renewable material in the tube body and shoulder—including 10% spruce wood recovered from sawmill waste (9).

Sana Packaging makes cannabis product packaging using recycled HDPE sourced by Oceanworks, which intercepts and recycles plastics that impact the ocean. "Our first run of reclaimed ocean plastic cannabis packaging removed four tons (8000 lb) of plastic waste from our oceans," said Ron Basak-Smith, co-founder and CEO of Sana Packaging (10). Sana Packaging also produces 100% plant-based cannabis packaging from hemp.

Recycled polyethylene terephthalate (PET) containers have been introduced by Bormioli Pharma. Made from 100% pharma-grade recycled content, the containers exhibit transparency and physical and mechanical properties equivalent to virgin PET (11).

AptarGroup is partnering with PureCycle Technologies to commercialize the latter's ultra-pure recycled PP for dispensing applications. PureCycle's patented recycling process, developed and licensed by Procter & Gamble, separates color, odor, and any other contaminants from plastic waste feedstock to transform it into resin with properties equivalent to virgin PP. "This critical partnership further reinforces our commitment to supporting a circular economy where products and materials are reused or recycled and do not become waste," stated Stephan Tanda, president and CEO of Aptar (12).

AptarGroup also provides lotion pumps for several products available via Loop and is a partner in the global circular shopping platform established by TerraCycle. With Loop, consumers purchase products in reusable packaging and they arrive in a returnable Loop tote. Once empty, the consumer replaces the container in the tote and schedules a pickup. Returned containers are cleaned, refilled, and readied to reship, creating a circular product experience (13).

Another Loop partner, RB, offers several over-the-counter products via Loop. The effort moves the company toward achieving its commitment to making 100% of product packaging recyclable or reusable by 2025. "Reusable packaging is the future of consumption," commented Nitish Kapoor, executive vice-president of the Health Business Unit for RB North America (14).

Renewable BioBase packaging is being launched by Sanner with the introduction of a 25 mm-diameter tube for effervescent tablets with matching DASG-1 desiccant closure. Biopolymers derived from renewable resources, such as bio-ethanol, achieve bio-based content above 90% and significantly reduce carbon dioxide emissions. "Bio-based packaging solutions have the same key characteristics as common packaging solutions; they can be processed on existing filling lines and can be recycled," says Peik-Christian Witte, director of R&D at Sanner. In addition, says Witte, "compared to common tubes made of fossil resources, this solution can increase shelf life of the tablets due to a higher water barrier performance, which is an additional value-add for our customers. These features support waste reduction for both the packaging solution and the packaged goods."

Sustainable packaging also is available for temperature-controlled shipments. The foam-free ClimaCell insulated liner from TemperPack now carries a How2Recycle label with the designation "Widely Recyclable." "Getting the How2Recycle certification will

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help ensure that anyone who receives a ClimaCell product will know that it can be disposed of alongside the cardboard box or paper bag it came in," said James McGoff, co-founder and co-CEO of TemperPack (15).

Liner thickness and density can be adjusted without major retooling to meet the needs of controlled temperature or frozen product. "ClimaCell liner options work with gel packs, ice packs, or dry ice and consist of a number of plant-based materials," says John Briney, director of marketing at TemperPack. The company uses a combination of materials, including starch, to increase the hydrophobicity of the insulation, and wraps the extruded insulation in coated paper.

"Overall feedback on ClimaCell has been great, especially in the specialty pharmacy industry," concludes Briney. "Most of the patients that were receiving [polystyrene foam] coolers had no easy way of disposing them and either stockpiled them or threw them away in their trash. We've received comments from a number of customers of how relieved they were to be able to recycle this new packaging, knowing it can be turned back into paper for other products."

References

1. AstraZeneca, "Leading with Health, Sustainability Report 2018," *www.astrazeneca.com,* accessed Nov. 20, 2019.
2. Bristol-MyersSquibb, "Waste," *www.bms.com*, accessed Nov. 20, 2019.
3. Bristol-MyersSquibb, "Product Stewardship," *www.bms.com*, accessed Nov. 20, 2019.
4. Bristol-MyersSquibb, "Household Generated Sharps Management Plan," *www.bms.com* (May 2019).
5. Merck, "Materials & Packaging," *www.msdresponsibility.com*, accessed Nov. 20, 2019.
6. Sustainable Packaging Coalition, "How2Recycle and Walmart Packaging Innovation Summit," GreenBlue November News and Updates, Newsletter, Nov. 21, 2019.
7. Walmart, "Walmart Announces New Plastic Packaging Waste Reduction Commitments," Press Release, Feb. 26, 2019.
8. Milliken, "jARDEN, SACMI, and Milliken Collaborate on Sustainable, Lightweight Pharmaceutical Barrier Bottles That Reduce Plastic and Energy Use," Press Release, May 9, 2018.
9. Hoffmann Neopac, "Neopac Introduces Tube Design Guide for Optimum Recyclability at CPhI Worldwide," Press Release, Nov. 25, 2019.
10. Sana Packaging, "Sana Packaging Launches New Line of Reclaimed Ocean Plastic Cannabis Packaging," Press Release, March 5, 2019.
11. Bormioli Pharma, "Bormioli Pharma to Bring Sustainability to the Pharma Industry with the First Compliant Green Plastic Packaging Solution," Press Release, May 10, 2019.
12. AptarGroup, "Aptar Enters into Strategic Partnership with PureCycle to Accelerate Integration of Ultra-Pure Recycled Polypropylene into Dispensing Solutions," Press Release, Sept. 3, 2019.
13. Aptar Group, "Aptar Announces Partnership with TerraCycle's Loop Platform," Press Release, Aug. 29, 2019.
14. RB, "RB Makes Popular Consumer Health Products 100% WasteFree," Press Release, May 21, 2019.
15. TemperPack, "TemperPack Partners with How2Recycle Label Program for Its ClimaCell Product Line," Press Release, Sept. 5, 2018. **PT**

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Employment Survey — *Article contin. from page 24*

Weighing the compensation factor

Salary ranked sixth on a list of 12 factors contributing to job satisfaction, up from ninth place in 2018. Compensation trailed factors such as challenging projects, intellectual stimulation, company's potential for success, a good work/life balance, and supportive management as the "main reason I come to work."

Satisfaction with compensation has trended downward during the past few years. More than 39% said they were paid fairly or excessively in 2019, compared with 41% in 2018 and 46% in 2017. In 2019, more than 40% of those surveyed said their pay was at the low end of the salary range for their expertise and responsibility; 17.6% said they were paid below market value.

The number of people reporting salary increases was stagnant from 2018 (54.1%) to 2019 (55.4%), following a drop from nearly 63% in 2017. The number of people reporting a decrease in salary ticked up from nearly 9% in 2018 to 11.4% in 2019.

More than one-quarter of respondents said they used their full allotment of vacation, personal, and sick time while 37% said they used less than half of the available time off.

Respondent profile

More than 220 bio/pharma professionals from around the world responded to the survey, which was fielded in November and December 2019. Respondents primarily were from innovator bio/pharmaceutical companies (31.3%), generic-drug manufacturing companies (13.3%), and contract research and manufacturing or consulting organizations (17.6%).

The respondents were involved in developing or manufacturing a range of drug types—with some listing multiple types—including small-molecule drugs (58.9%), large-molecule drugs (45.1%), vaccines (19.8%), cell therapies (17.8%), gene therapies (17.8%), and nutraceuticals (17.3%).

Respondents work at small and large companies and are responsible for R&D, process development, technology transfer, validation, quality control/assurance, formulation, manufacturing, and other functions. Nearly 40% of the respondents held a doctorate or higher degree; more than one-third held at least a Master's degree.

Compared with previous years, the respondents had slightly less experience working in the bio/pharma industry; 26.9% had fewer than 10 years of experience, 25.6% had 10–20 years, 36.9% had 20–35 years of experience, and 12.1% have worked in the industry for more than 35 years.

Respondents working in the small-molecule drug arena worked more hours compared with peers in the biologic-drug segment. More than 37% reported working more hours than the previous two years, compared with 30.7% for the biologics workers.

References

1. *Pharmaceutical Technology*, 2019 *Pharmaceutical Technology/BioPharm International* Employment Survey, December 2019.
2. *Pharmaceutical Technology*, 2018 *Pharmaceutical Technology/ Pharmaceutical Technology Europe* Employment Survey, December 2018.
3. *BioPharm International*, 2018 *BioPharm International* Employment Survey, December 2018. **PT**

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