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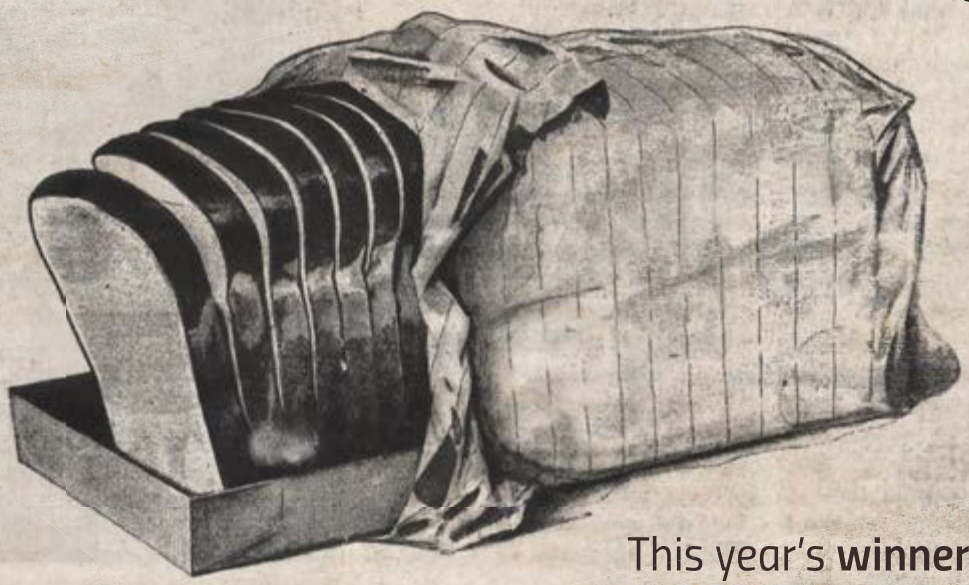
2019 Pharma Innovation Awards!



This year's **winners** offer **slices of innovation**

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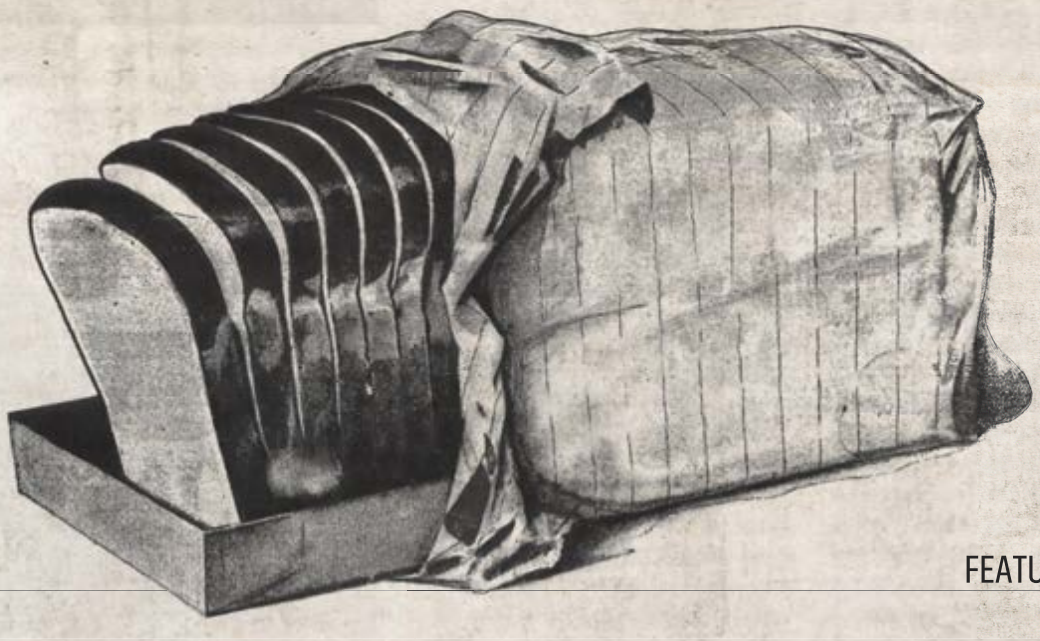
WINNERS!

2019 Pharma Innovation Awards!



FEATURES

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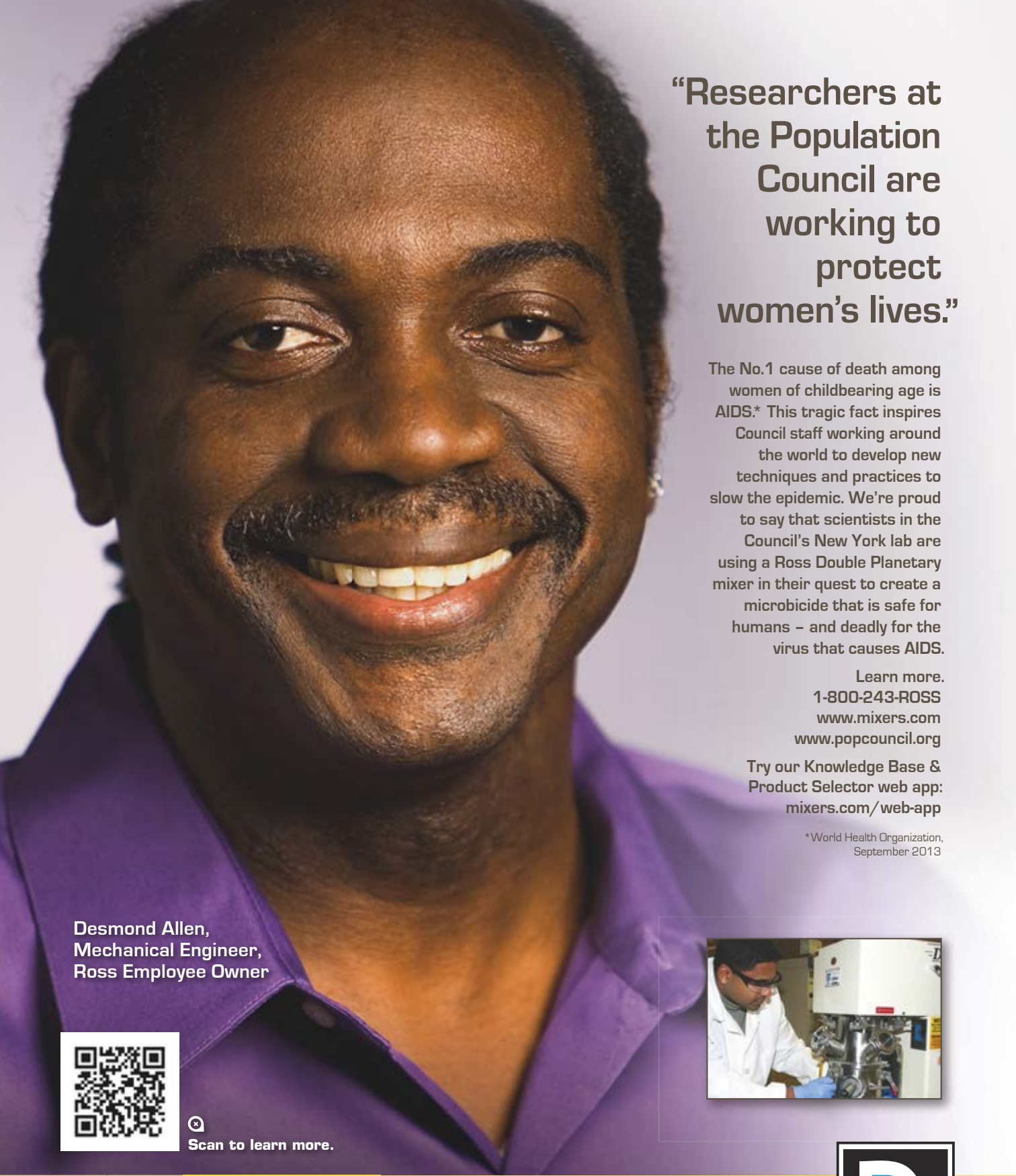
Pharma Manufacturing™ (USPS number 023-188) (ISSN number 1550-6509) is published 10 times a year by Putman Media Inc. (also publishers of Food Processing, Smart Industry, Chemical Processing, Control, Control Design, Plant Services and The Journal), 1501 E. Woodfield Road, Suite 400N, Schaumburg, IL 60173 (Phone: 630-467-1300 Fax: 630-467-1120). Periodicals Postage Paid at Schaumburg, IL and additional mailing Offices. POSTMASTER: Please send change of address to Putman Media, PO Box 1688, Cedar Rapids IA 52406-1888. Phone: 1-800-553-8878 ext 5020. SUBSCRIPTIONS. To receive a complimentary subscription go to www.pharmamanufacturing.com. Subscription rate for non-qualified U.S. subscribers is $68/yr. Single copy rate is $15.00. Other international is $200/yr (airmail only). Canada Post International Publications Mail Product Sales Agreement No. 40028651. Canada Mail Distributor Information: Frontier/BWI, PO Box 1051, Fort Erie, Ontario, Canada L2A 5N8.



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*World Health Organization, September 2013

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How you slice it

The definition of innovation isn't always clear cut

Finding an innovative approach to discussing innovation is not easy. The word itself has been overused, as have all of the ways in which people describe innovation (such as "the greatest thing since sliced bread").

That being said, I'm quite fascinated by the origins of sliced bread (I also really like bread). Pre-sliced bread was simultaneously an innovation benchmark and an example of incremental improvement. On the one hand, it was groundbreaking: Prior to the 1920s, bread had been a source of nourishment for centuries without the interference of mechanization. But the '20s were a decade marked by a vibrant consumer culture, where people sought out more leisure time and were willing to spend money on products that facilitated convenience. The concept of packaged, uniformly sliced pieces of bread was disruptive for many (especially the unfortunate homemakers who had been stuck manually attempting to evenly cut slices of bread for the entire family) and soon became indispensable.

Yet at the same time, sliced bread is also a tale of persistent, incremental improvements. Despite the fact that the original inventor of the automatic slicer, Otto Frederick Rohwedder, took great pains to get it right (rumor has it he even sought feedback from homemakers to determine how thick to cut the slices), his loaves were sloppy and often fell apart. A St. Louis baker named Gustav Papendick bought Rohwedder's second machine and made it better. Papendick's improved design packaged the sliced loaves in cardboard trays, keeping the bread neat and orderly.

This forward leap in the baking industry could not have happened without those willing to reimagine ways in which equipment could meet consumer needs, as well as the persistent efforts of those looking to incrementally improve on the slicer technology.

As B2B editors, much of our time at industry events is spent learning about new equipment and services designed to meet the specific needs of pharma. We hear all the stories behind this innovation and thus truly understand and appreciate the investment pharmaceutical equipment vendors put into developing and improving their products. We believe all types of innovation, whether earth-shattering or incremental, should be recognized. And over the course of a year's worth of industry events, our editorial team has amassed quite a collection of winning technologies.

This month's cover story is a tribute to those who listen to the needs of the market and their customers, and as a result, have distinguished themselves as leaders in pharmaceutical equipment and technology. It's true that not everything can be the greatest thing since sliced bread. But the bread and butter of innovation is its ability to create value and deliver that value to a community of users in the form of a much-needed solution.

This year, we have highlighted 19 winners, spanning across five different categories. Please take the time to read through our annual Pharma Innovation Awards in this issue. We promise that our slices of innovation will keep your manufacturing process fresh.

industry dose

It starts with one

BIO 2019 shows how incremental investments make a global impact

Earlier in June, Philadelphia hosted the Biotechnology Innovation Organization's 2019 BIO International Convention. The event, which touts itself the "world's largest meeting for the pharmaceutical and biotechnology industries," delivered on its promise, hosting more than 17,000 attendees and 1,800 exhibitors (now if only Philly had enough hotel rooms to accommodate).

With this conference, BIO affirmed its commitment to lead an industry-wide effort to promote inclusion and diversity. The event had a truly global feel, with the show floor organized by country, indicated by large banners above. The goal was to create an environment where diverse professionals could collaborate, and where different ideas and approaches were welcomed. This fueled the conference's theme of "it starts with one," creating an event where the daily efforts of attendees were celebrated.

New chair, new direction

The event featured an address from BIO's new chair, Jeremy Levin, CEO of Ovid Therapeutics. "Our covenant requires that we take the risks necessary and aspire to find and develop the best possible medicines," said Levin to a packed room.

The newly elected leader indicated that his tenure will bring a focus on drug development and policies related to rare diseases — an area familiar to Ovid, a biopharma company committed to developing treatments for people with rare neurological disorders. An estimated 30 million Americans live with rare diseases — with 90 percent of those lacking an FDA-approved treatment. The "risk" is that rare disease drugs pose broad challenges in terms of clinical research, patient recruitment, and long development timelines.

Calling out bad actors

Levin was among several speakers who addressed the drug pricing issue. Levin spoke about industry "bad actors" who "inflate prices because they can — without any change in value." Levin proposed more frank and honest conversations with patients, saying pharma has a responsibility to "call out and distance ourselves from bad actors in our industry who taint us all."

The same sentiments were echoed by Merck CEO, Ken Frazier. "The benefits from our medicines are tremendous but the cost issue needs to be solved," said Frazier.

Frazier said his role as a leader is to optimize both patient access and profits, not to maximize profits. "No company just driven to maximize profit will last — you have to have a higher purpose," said Frazier.

Riding the innovation wave

Gene therapies remain top-of-mind in biopharma as the industry transitions the field from experimental to commercial — and there was no shortage of buzz around the topic at BIO 2019. While only a handful of gene therapies have received a regulatory nod in the U.S., agency leaders estimated that by 2025, the FDA will be approving 10-20 new cell

PHARMA HAPPENINGS

Upcoming notable industry events

The 13th Digital Pharma East

Sept. 17-20 | Philadelphia, PA
Hear from leading international speakers on a range of topics meant to help pharma conquer innovation challenges – from improving data analytics to bridging digital organization gaps.

PACK Expo

Sept. 23-25 | Las Vegas, NV
Bringing packaging suppliers together with end users from every vertical industry, the expo will be the largest, most comprehensive packaging event of the year.

ISPE Annual Meeting and Expo

Oct. 27-30 | Las Vegas, NV
Pharma professionals from all levels of the industry come together for sessions on supply chain management, facilities and equipment, information systems, industry innovations and more.

ISPE

CPhI Worldwide

Nov. 5-7 | Frankfurt, Germany
One of the biggest pharma events of the year brings together 45,000 professionals from around the world for educational seminars, networking, and exhibits from more than 2,500 pharma companies.

CPhI worldwide

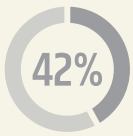
and gene therapy products per year. During his BIO fireside chat, Frazier emphasized Merck's strong interest in gene therapy, calling it the "next wave in innovation."

The optimism, however, was balanced by discussions of the numerous challenges that still remain. A gene therapy panel noted specific issues in gene therapy development and commercialization, such as the need for a different regulatory framework, the shortage of skilled workers and high manufacturing costs.

The topic was appropriate for the conference's location, since the Philly region is emerging as a hotbed of biotech innovation, with more than two dozen cell and gene therapy companies in the area.

Pharma's biggest process data challenges

struggle with validation of system



still have some data on paper

New research report available!
www.pharmamanufacturing.com/DataSurvey2019

DON'T MISS ONLINE

10 of the highest paid CEOs in pharma
Lucrative compensation packages for CEOs are certainly not unique to pharma. But many of the industry's top dogs got hefty raises last year, showing it's a good time to be a CEO in pharma.

Biosimilars are coming to LATAM
There is a flourishing biosimilar industry in Latin America with its own research, development, production and commercialization capacity.

The top 5 drugs bound for blockbuster status
A wave of incoming anti-inflammatories and gene therapies that could make it big in the next five years.

FDA DSCSA Pilot Project Program
A Q&A with John Jacey, a leader on TraceLink's Digitization Strategy team.

Karen Langhauser
Chief Content Director

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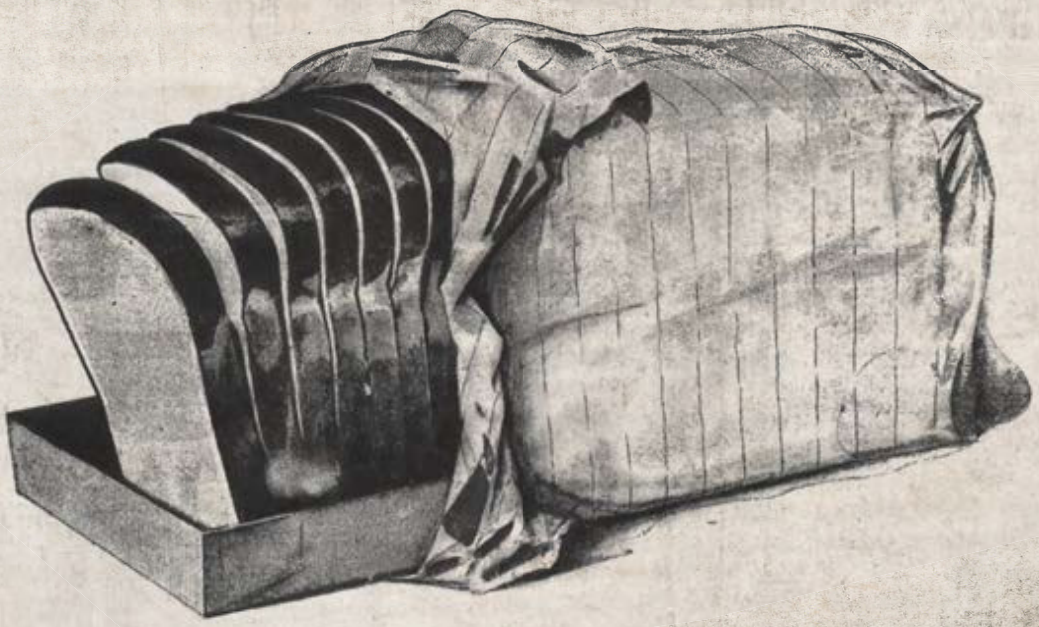


This year's **winners** offer **slices of innovation**

Ironically, the phrase used to praise an innovative new product — "the greatest thing since sliced bread" — has become so unoriginal that it's cliché.

In the 1920s, however, the convenience of commercialized pre-sliced bread was what the American food consumer wanted — and after the first machine appeared in 1928, equipment manufacturers and bakery industry experts got to task, improving and adding to the existing designs.

This forward leap in the baking industry could not have happened without rethinking what equipment can do, and the persistent efforts of those looking to incrementally improve on this innovation.

Here at *Pharma Manufacturing,* we understand and appreciate the investment pharmaceutical equipment vendors put into developing and improving their products. All types of innovation, whether earth-shattering or incremental, should be recognized. This month's cover story is a tribute to those who listen to the needs of the market and their customers, and a result, have distinguished themselves as leaders in pharmaceutical equipment and technology.

With that said, we are proud to introduce this year's **Pharma Innovation Award** winners: recently launched or updated technologies and systems that, based on their technical and practical merits, were selected by *Pharma Manufacturing's* editors and reviewers.

2019
PHARMA INNOVATION AWARDS

BIOPROCESSING

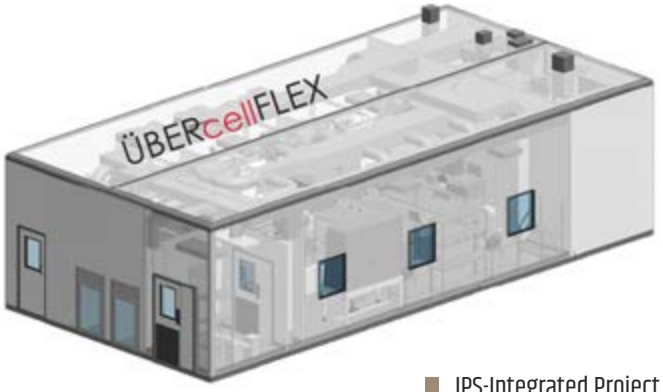
It's an exciting time of growth for biopharmaceuticals. The number of biopharma players, marketed products and classes of therapies continues to expand. With this expansion comes new demands for the industry. Intuitive vendors are recognizing that their biopharma customers are juggling regulatory uncertainty, cost pressures, and growing pipelines of molecules.

As much of the industry is looking towards more continuous manufacturing and more modular construction, our bioprocessing category winners are those who are helping their customers meet these challenges — offering solutions that are compact, flexible and speed products to market.

Our first winner truly embraces the idea of next-generation bioprocessing. MilliporeSigma has a reputation for listening to its customers and developing products accordingly, and the **BioContinuum Platform** delivers on that promise.

Next-generation bioprocessing is about targeting high productivity, high intensity processes. This platform is a unique and holistic approach to next-gen bioprocessing that allows users to realize the benefits of process intensification throughout the entire process. The platform is an evolving and convergent portfolio of advanced processing and software, automation and analytics technologies, applications and expertise that will enable customers to confidently enter this new era of manufacturing.

MilliporeSigma's
BioContinuum Platform



IPS-Integrated Project Services and G-CON Manufacturing's
ÜBERcellFLEX PODS

What makes it especially flexible is that MilliporeSigma recognized that not all biomanufacturers are on the same path. For some, the focus is on improving unit operation's interoperability. For others, the goal is fully continuous processing. No matter what your path, the BioContinuum Platform aims to provide the building blocks for success.

Our next winner is the result of two industry vets teaming up. IPS-Integrated Project Services and G-CON Manufacturing collaborated to produce the **ÜBERcellFLEX** — a pre-fabricated modular cleanroom infrastructure for the manufacturing of autologous cell therapies.

Available in both 12- and 24-foot wide POD configurations, the processing suites enable faster and more predictable project schedules for new facility construction and a standardized solution to meet speed to market requirements — filling a major need in the cell therapy arena. Multiple units can be installed to scale up/out from phase one clinical production to commercial manufacturing. The PODs can also be ready to order, in either open or closed-processing format, with little engineering time and no additional engineering when PODs are reproduced as part of scale up.

ÜBERcellFLEX is part of the iCON product line, which also offers platforms for other applications, including fill/finish and monoclonal antibodies.

Our final winner is a newer kid on the block. Univercells announced the commercial launch of its proprietary **NevoLine** bioproduction platform for vaccines in early 2019. The technology platform was developed by Univercells, and was part of a $12 million Grand Challenges grant awarded by the Bill & Melinda Gates Foundation to apply it for the production of affordable inactivated polio vaccines (sIPV).

By designing integrated process architecture to reach miniaturized, high-capacity production capabilities, the NevoLine platform enables sustainable and flexible production. Through intensification and chaining of unit steps into a continuous process, users achieve high yields with less time and money invested.The system is self-contained into a 10m² series of isolators. To put it in perspective, a facility designed with four NevoLine units would deliver up to 50 million sIPV doses per year for an estimated capital cost of $20 million.

The company also recently announced it had been awarded a second grant by the Bill & Melinda Gates Foundation and will be adapting the process design of the NevoLine platform to deliver affordable measles and rubella vaccines.

SMART PHARMA

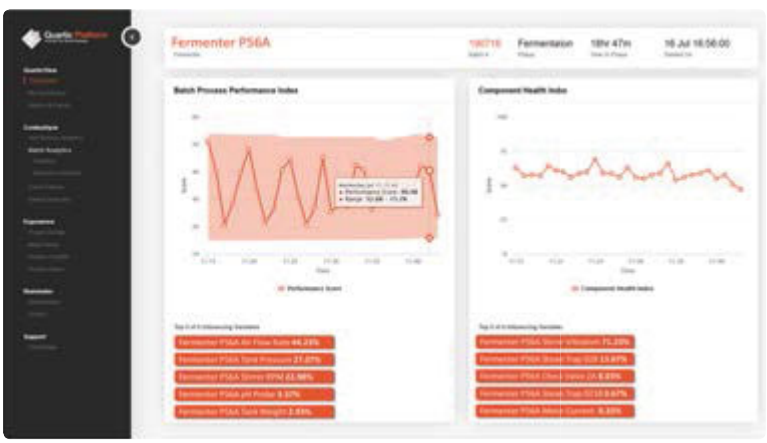
Smart pharma gives biopharma a run for its money in the competition for the industry topic with the most hype (and certainly wins for the most buzz words). Industry 4.0, digital transformation, IIoT — whatever terms you want to use, the movement toward a more digital industry is slowly but surely underway. But there are still significant hurdles that need to be overcome for the benefits of digitalization to be captured across the highly regulated, traditionally risk-averse pharmaceutical industry.

The concept of smart pharma is broad and the winners in this category run the gamut from virtual reality to material handling, but all are united by the integration of smart technology into their products to help manufacturers on their digital transformation journeys.

As pharma looks to build sustainable digital manufacturing solutions, two challenges they face are making data generated by legacy assets and operational technology (OT) systems ready for artificial intelligence (AI) and acquiring the right data science and programming skills. To this end, the first winner in this category comes from Quartic.ai — a newcomer founded by a veteran team of process manufacturing and data scientists determined to make AI deployment easy.

The **Quartic Platform** delivers on this mission, offering an AI-powered smart manufacturing platform built specifically for OT users. Operating on the premise that AI application can only deliver results for manufacturing if it is built and used by those who understand the manufacturing equipment and processes best, the new platform looks, feels, and behaves like the OT systems with which manufacturing experts are familiar.

The platform, which supports distributed deployment at the Edge, Fog and Cloud, is comprised of two key components: the Quartic illuminator — an IIoT data pipeline that dynamically creates asset context for data from IIoT, OT, MES and ERP information and makes its analytics ready; and the Quartic eXponence — an engine that creates asset intelligence through advanced analytics combined with the power of automated machine learning.



Quartic.ai's Quartic Platform

Next up is another example of a company that used its expertise to develop a product specifically suited to fill a need in the pharma industry. The **Virtuosi** education platform is the brainchild of Quality Executive Partners (QxP), a management and compliance consulting company.

Virtuosi is an educational platform, featuring multifaceted digital technologies including immersive virtual reality (VR) interactive experiences. Digital courses, called "episodes," include knowledge and process checks across a progression of topics. The powerful impact of VR on enhanced learning is based in behavioral learning theory. Interactive immersive VR experiences with the body and not just the mind allows learning to be embedded into the long-term memory centers of the brain, increasing recall.

Software containing the digital courses are downloaded from a central server, allowing continuous updates as regulations and life science technology changes. Each VR workstation includes a high-speed gaming computer, virtual reality headset and hand controllers, and two motion sensing devices. The first series available focuses on sterile products manufacturing and microbiology, but future series will offer education in regenerative medicine,, biotech, combination products, solid dose, semi-solid and liquid products, and APIs.

Manufacturing excellence requires fully digitized production records and

processes so that all departments can seamlessly be connected. Yet, survey after industry survey reveals that most pharma production environments still depend on error prone paper-based production records, contributing to poor resource utilization, inefficient processes, higher deviation rates and delayed product releases.

MasterControl's new **Manufacturing Excellence** solution (so new that is still has that new software smell) aims to bridge the gap between operational excellence and smart manufacturing by automating the last mile of production. The software enables manufacturers to remove remaining paper from the shop floor to ensure that production record reviews and releases are fully digital, connected and accelerated. The cloud-based solution eliminates preventable errors, long review cycles and costly waste created by manual data entry processes.

The Manufacturing Excellence solution has a patent-pending builder

Quality Executive Partners'
Virtuosi education platform

tool allowing organizations to configure the digital solution to their existing processes, streamlining both implementation and adaptability. The builder tool houses the global elements of the manufacturing processes, allowing users to update once and have information propagated throughout the system.

Ceremoniously bumped out of the packaging category, our next winner offers an incremental, yet important next step in labeling technology. Helping the packaging sector take strides towards adopting smart factory technologies, the **HERMA 500** label applicator from HERMA U.S. is an IIoT-enabled machine utilizing real-time metrics to optimize production efficiency and consistency, even in a multi-factory setting.

HERMA U.S.'
HERMA 500 label applicator

The next-generation label applicator builds upon its predecessor's best features and integrates Industry 4.0 connectivity. Remote access via web browsers allows for off-site operation and, on-site, the machine's user interface displays intuitive pictograms on a 4.3-inch touchscreen. A variety of optional upgrades can be accessed by simple code activation, and the unit's firmware is automatically uploaded via ethernet.

Fittingly, the machines are being produced in HERMA's new state-of-the-art Labeling Machinery Division facility, recently relocated to its headquarters site in Germany.

Our final winner also brings smart technology to new areas in pharma. Touting itself as the market's first Industry 4.0 ready vacuum lifter, PIAB's **piLIFT SMART** delivers on the promises of Industry 4.0. by offering smart data features based on internet connectivity.

Sensing and monitoring movements and responding quickly to user intentions, the vacuum lifter will lift and weigh loads simultaneously, collect and log data, making process statistics and analyses immediately accessible to the user through web platform log-in.

With capacity to lift objects weighing 90 pounds, the piLIFT SMART offers top-notch vacuum lifting technology to customers in a broad range of industries.

MONITORING AND ANALYTICAL DEVICES

As one of the world's most heavily regulated industries, pharma has always required accuracy, reliability and repeatability. Today's complex products are driving new trends in manufacturing, such as single-use and continuous. This transformation requires new points of measurement delivered by improved instrumentation.

Emerson's
Rosemount 550pH sensor

Our first nod in this small but vitally important category goes to Endress+Hauser's **iTHERM TrustSens,** touted as the world's first self-calibrating temperature sensor. New quality standards in biopharma mean calibration of critical measurement points is typically required every six to 12 months. E+H's technology makes it possible for a sensor to perform a self-calibration that will automatically detect drift and determine if manual attention and adjustment is warranted. This can significantly reduce risk and increase efficiency for the facility.

The technology relies on the Curie point physics principle and fixed-point calibration method normally employed in lab environments. It enables reliable, secure automated calibration monitoring and electronic record management, including record creation, archiving, and transmission as specified in the FDA 21 CFR Part 11 — effectively eliminating the need for manual intervention.

A facility's calibration monitoring solution can be comprised of up to 20 iTHERM TrustSens TM371 or TM372 temperature sensors, all connected via HART communication.

Sharing the accolades in this category is Emerson's **Rosemount 550pH** sensor.

As the industry shifts from traditional stainless-steel bioreactors to disposable plastic bags, facilities need reliable sensors for vital liquid analysis. Pharma wants the flexibility of single-use methods, but also wants to achieve process control in the same way as with stainless-steel methods, with no degradation in performance. Emerson, with a long history of producing innovative technology, has stepped in provide a possible solution.

The 550pH sensor is an electrochemical, fully disposable device with sensor stability of less than 0.005 pH change per day verified by extensive testing. The single-use sensors perform as well as or better than those used in stainless-steel bioreactors. Wherever possible, Emerson maintained industry-standard designs, eliminating the need for additional training. Added features, such as wet storage, overcome challenges that have long been plaguing single-use processing.

Facilities can now experience all the benefits of single-use bioreactors without having to compromise in liquid analytical instrumentation.

PLANT OPERATIONS

When it comes to operational excellence, the plant floor offers immense opportunity for companies looking to gain a competitive edge. The winners in this category bring significant improvements in efficiency and flexibility, with an even stronger focus on quality and safety.

Interestingly enough, despite the current buzz surrounding biopharmaceuticals, all of the plant operations winners are related to tablets and capsules. The fact that new advancements are still being made in solid dose is no doubt a contributing factor to the sector's longevity.

Kicking off this category is one of the more unique technologies in this year's group of winners. The use of high potency active pharmaceutical ingredients (HPAPIs) is increasing, as pharma strives to focus on developing more targeted, effective treatments. This means manufacturing often involves handling toxic or highly sensitive solids that can pose a direct threat to worker safety. Rommelag, who you might recognize as the first company to introduce blow-fill-seal technology to the U.S., has stepped up to the plate with its **Flecotec** single-use containment system, enabling consistent containment from API to production.

The system's core components consist of the company's Flecozip and Flecotric. Flecozip acts as the contamination-free interface between process units and containers, while Flecotric makes it possible to adapt the system to virtually all common equipment and processing units.

Allowing for both primary containment to the mid-nanogram levels, as well as secondary containment with similar or increased performance, the system has been installed in new applications as well as used

Qualicaps'
QUALIS-UVS laser printer

as a direct replacement for lesser performing, existing equipment. In addition, because Flecotec is all about single-use containment, once a process step has been completed, the entire system is simply disposed of — keeping cleaning and validation to a minimum. The system reliably protects workers and the product from contamination, while also allowing protective clothing to be eliminated in many work areas.

Making its colorful world premiere at Achema 2018, Fette Compacting's **FEC20** capsule filling machine allows each individual capsule filling process step to be controlled and monitored separately. With this machine, the company has adapted and further developed the technical concept of its FEC40 unit (released in 2016) in order to make it available for medium-sized batches of up to 200,000 capsules per hour.

Prior to the FEC series, the assemblies in capsule filling machines were controlled by mechanical coupling. By using servo and torque motors, the new machine decouples individual process steps. What this means is that optimal parameters for each process step can be defined, thereby improving both quality and output per time unit. The machine's database contains all formulations and user process parameters, while the system automatically and immediately examines each entry for consistency.

The patented removal system of the tamping pin station together with the hygienic design reduces the time for a changeover. This enables the user to swiftly change between products as well as between dosing methods.

Next we have Key International's **Enclony PLANET 6G**, a state-of-the-art, high-speed automatic tablet and capsule visual inspection machine. The inspection machine's 10 interdependent 2D cameras and two additional 3D cameras take 14 pictures of every tablet or capsule that passes through the machine, checking them back to a "golden" image. Each tablet is captured from eight precise angles, eliminating blind spots. Defects are compiled so that users can improve their process.

The Enclony's jam free sorting, smart HMI, humidity and temperature sensor, and four-sided wing door capability enable it to produce as many as 350,000 tablets per hour and 150,000 capsules per hour. Key says that the machine can be programmed for new products in just 30-35 minutes, as the intuitive Smart HMI guides the operator thorough the process. Additionally, the company boasts that the machine can cover 95 percent of product sizes and shapes on market with the tools included.

Closing out this category is Qualicaps' **QUALIS-UVS** laser printer. A viable alternative to traditional ink printing, UV laser imprinting has many benefits, including the elimination of defects caused by ink, flexible design options, operational efficiency and larger print surface.

Fette Compacting's
FEC20 capsule filling machine

Qualicaps, perhaps most well-known for its range of capsule offerings, has proven that it can also offer innovation in laser printers. The QUALIS-UVS imprints on tablets or capsules at a speed up to 400,000 per hour — the company boasts this is one of the fastest UV laser printers in the world. The new machine is more compact than the company's existing UV laser printer (LIS-250D), includes a built-in blower, and requires fewer change parts. Marking letters, marks or logos can be made by CAD software, allowing for flexibility in design.

PACKAGING AND HANDLING

Today's complex and high potency drug formulations require that packaging and packaging equipment evolves. Many newer drugs are temperature sensitive, unstable and/or vulnerable to contamination, making packaging design more difficult — but packaging suppliers have stepped up to the task. Our largest and most diverse category brings several cross-company collaborations, resulting in targeted solutions to new industry packaging challenges.

As the industry produces more potent APIs, larger molecules and modified release profiles, there is increased risk for stability issues associated with moisture, oxygen and volatile reactives. Innovative dosage forms, such as chewable and disintegrating tablets, also face significant shelf life challenges with respect to humidity sensitivity. Recognizing the complexity of matching moisture- and oxygen-sensitive medicines to ideal packaging solutions, Aptar CSP Technologies launched the **Xcelerate** services suite.

An innovation favorite among our evaluators, the suite optimizes the active packaging development process through end-to-end expert insight, resulting in expedited speed to market for moisture- and oxygen-sensitive medicines. Xcelerate combines Aptar CSP's groundbreaking active packaging with technology from FreeThink Technologies, a contract research organization with expertise in stability.

Xcelerate services are designed to significantly condense the entire active package design, testing, and implementation process — often by months, according to the company. The comprehensive, hands-on approach also includes capabilities to produce clinical trial and stability samples, regulatory support and consulting and testing during commercial implementation.

Our next winner is a joint cross-company development project from groninger, known for its high-precision filling and closing machines and SKAN, experts in cleanroom equipment and isolator design. Recognizing that processing aseptic and high potency products requires increased safety for operating personnel, optimized machine design for shortest set-up times, and optimum accessibility for machine operation and cleaning, the duo produced a unique line concept for vial processing.

groninger and SKAN's
INTEGRA isolator line

Making its debut at ACHEMA 2018 (and also taking home an ACHEMA Innovation Award), the **INTEGRA** line integrates both an isolator and filling machine.

INTEGRA was developed with a focus on processing toxic products. Thanks to the integration of the filling machine into the isolator and the integration of the SKANFOG decontamination system, the entire line can be cleaned and decontaminated in approximately 30 minutes with optimum accessibility for the operating personnel.

Increased security and support for format changes is made possible by the use of QR codes, which give operators a better overview of position, installation order and recipe assignment.

The integrated lines are available with different line speeds up to 400 objects/minute and with oRABS or standardized isolator technology.

Our next three winners fall into the drug delivery and device portion of this category. Starting with another collaboration, the **SteriDrop** tube combines the trusted barrier properties of Neopac's proprietary Polyfoil tubes with an Ophthalmic Squeeze Dispenser from Aptar Pharma (part of the same AptarGroup as the first winner in this category). Designed for eyedrops, the packaging eliminates the need for preservatives, such as Benzalkonium Chloride, which can lead to side effects with chronic use.

The tube's mechanical system releases a precisely measured drop when pressure is exerted on the tube, and prevents the liquid from flowing back into the tube, thereby guaranteeing a level of microbiological safety previously unattainable. Introduced at CPhI Worldwide 2018, the SteriDrop tube has proven highly conducive to protecting preservative-free eyedrops from contamination before, during and after initial consumer use.

Neopac's
SteriDrop tube

Recognizing the need for exacting packaging requirements to protect against interactions between drug and container, our next winner has produced a new generation of ultra-pure pharmaceutical vials. Designed as a modular concept, SCHOTT's **EVERIC** vials provide pharma companies with a unique combination of attributes to package biologic drugs while supporting today's fill-finish quality requirements.

EVERIC pure, the first feature available, is designed for sensitive drugs and drugs with low filling volumes. The vials ensure drug stability by using an improved Borosilicate glass tubing.

Thanks to their better chemical resistance, the vials show a very low concentration of leached glass elements even for low fill applications — a major advantage over aluminosilicate vials. As a result, the new vials provide a tool for pharma companies to keep delamination under full control.

In the future, pharma companies will be able to add more features to their vials to improve the drug filling and transportation process. EVERIC strong vials will better withstand side compression and axial load during filling and transportation and EVERIC smooth vials will offer coating on the outer surface.

The final spot in this category goes to BD Pharmaceutical Systems for its **BD Hylok** syringe.

High pressure exerted on syringes during injection of viscous solutions can cause needle disconnection and connector rotation, which can lead to leakage. The BD Hylok glass pre-fillable syringe is a new luer syringe for the administration of viscous and intravenous drugs — and according to the company, it's the first glass pre-fillable syringe validated for delivery of IV drugs.

SCHOTT's
EVERIC vials

The syringe offers customers the advantages of glass containers (inertness and resistance to steam sterilization), with a strong and robust luer connection. The main applications for the BD Hylok syringe are hyaluronic acid (dermal fillers, intra-articular) and IV injection. However, it is compatible with main needles or IV connectors, allowing it to address a wide array of medical needs across the health care and medical aesthetics markets.

And there you have it — the **2019 Pharma Innovation Award** winners — the greatest things since last year's winning technologies. Congratulations and thank you for listening to the needs of the industry and your customers, and tirelessly pushing to make pharma better.

Jessica Rayser
Product Manager, Accugenix Services,
Microbial Solutions, Charles River

Lucia Ceresa
Senior Product Specialist,
Microbial Solutions, Charles River

Qualifying your cleanroom

Revised GMP guidelines will strengthen emphasis on contamination control, impacting cleanroom performance qualifications

Technology, manufacturing processes, and regulatory trends have changed in the 10 years since the last revision to Annex 1 of the EU GMP Guideline for the Manufacture of Sterile Medicinal Products. With the revised document set for release this year, the updates significantly impact quality control (QC), quality assurance (QA), and all laboratory activities. This revision is intended to add detail and clarity and provide global alignment of standards. Even though Annex 1 is a European document, drugs manufactured globally for sale in the EU need to comply with the standards, which is why Annex 1 was developed in collaboration with global regulatory bodies such as the World Health Organization and Pharmaceutical Inspection Co-operation Scheme.

Moreover, with the current economic boom for pharmaceuticals, more companies are expanding their manufacturing capabilities and opening new facilities. This is particularly relevant as, according to a survey from the Parenteral Drug Association, industry members find the most challenging proposed change in Annex 1 to be the qualification of facilities.

Constructing and qualifying a new cleanroom is a huge investment of a company's money, time, and resources. Given the purpose of the cleanroom and its role in product quality, there are extensive regulatory requirements surrounding cleanroom design and validation. With recent revisions to some of these requirements in ISO 14644 and proposed changes to Annex 1, will your qualification meet the new standard?

Maintaining compliance

A recent U.S. Food and Drug Administration warning letter highlighted the potential consequences of failing to comply with GMP standards. In the letter, the FDA made the following observations regarding facilities and contamination control:

> *Drug products intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA.*

> *Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).*

> *Your firm failed to maintain the buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition (21 CFR 211.56(a)).*

> *Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).*

To maintain a strong compliance position, it is imperative to start with a solid foundation. A well-functioning cleanroom starts with good process and cleanroom design and utilizes key aspects of the well-established quality by design (QbD) methodology (Exhibit 1) and Quality Risk Management (QRM). The overall contamination control strategy should already be established and incorporated into the design. The appropriate layout, space, equipment, building materials, and facilities need to be determined based on the type of product and manufacturing cycles.

EXHIBIT 1

Quality by Design Methodology

The flow of personnel and materials are critical aspects that also require special consideration. Annex 1, 2017 draft version section 4.2 states "the maximum number of operators in critical areas should be determined based on QRM, documented in the contamination control strategy, and validated during activities such as initial qualification and aseptic process simulations, so as not to compromise sterility assurance." It is critical to control people and materials entering the classified clean areas.

The role of the QC microbiologist

The cleanroom design and qualifications should be overseen by a team representing (but not limited to) Engineering, Operations, Quality, Facilities and Microbiology. The Annex 1 draft from 2017 emphasizes the role of the QC microbiologist for all manufacturing processes. Specifically, in terms of cleanroom qualifications, it states in 2.c that "processes and monitoring systems for sterile product manufacture must be designed, commissioned, qualified and monitored by personnel with appropriate process, engineering and microbiological knowledge."

It is important to recognize the many tasks of the QC microbiologist and their responsibilities during the planning and setting up a new cleanroom. While QC microbiologists are integral to the manufacturing design and processes, they are also the primary owner of the microbiology laboratory. Their overall list of responsibilities is comprehensive and might look similar to this:

- Design the laboratory and workflow
- Order, install and qualify equipment
- Hire and train technicians
- Write and revise SOPs
- Develop an environmental monitoring program
- Establish sampling plans
- Implement and validate QC methods and testing based on release specifications
- Conduct bioburden and endotoxin testing
- Perform microbial identifications
- Investigate out of specifications, deviations and contamination events
- Manage LEAN activities and productivity projects

After the cleanroom design, installation, and operational qualifications, the QC microbiologist takes the lead for the cleanroom performance qualification. The process performance qualification (PPQ) studies determine whether an initial state of control has been established. For example, the FDA stated in a warning letter, "Successful PPQ studies are necessary before commercial distribution. Thereafter, ongoing vigilant oversight of process performance and drug product quality is necessary to ensure you maintain a stable manufacturing operation throughout the drug product lifecycle."

The performance qualification is when the surface and airborne particulate and bioburden levels are monitored and tested (see Tables 1 and 2). The qualification is absolutely essential for determining whether the cleanroom was adequately designed and built to prevent contamination of the products being manufactured and requires thorough microbiological analyses. A poor qualification increases risk to manufacturing, the environment, patient safety, and the company's investment in the new facility.

Revised guidelines

The revised Annex 1 treats Class A (class 100/ISO 5) and Class B (class1000/ISO 7) equally in terms of monitoring and requalifications. These areas will need a higher number of sampling points for the aseptic processing and the immediately adjacent environment (grade A/B) (Annex 1, 2017 draft version: 5.26). Sampling points should include all critical processing locations, based on risk to the final product. The larger number of sampling points can contribute to a better understanding of the state of control and potential changes and trends.

Accurate microbial identifications

During performance qualification, the bioburden counts need to be followed by microbial identification. Understanding the flora in the manufacturing environment serves to direct an appropriate cleaning strategy, helps determine where the contamination is coming from and what controls need to be added to protect the product. Risk assessments are an important part of qualifications, and an appropriate risk assessment cannot be made without an accurate identification.

The identifications generated during cleanroom performance qualification establish a baseline as to what flora is found in the manufacturing environment, and are also critical for establishing alert and action limits. From this information, changes in the manufacturing environment can be assessed.

A cleanroom technician performs HEPA filter leak test.

According to Annex 1, 2017 draft version: 9.33, "If microorganisms are detected in a grade A or B zone, they should be identified to the species level and the impact of such microorganisms on product quality (for each batch implicated) and state of control should be evaluated. Consideration may also be given to the identification of grade C and D contaminants, and the requirements should be defined in the contamination control strategy." It cannot be understated how important the accuracy and reproducibility of the microbial identifications are, especially for the initial qualification as it serves as a baseline.

Moreover, the cleanroom qualification is not a one-time event. Cleanrooms should be requalified biannually, as well as after changes to equipment, facilities or processes. It is clearly stated in the reviewed Annex 1 guideline (section 5.29) that for grades A/B the maximum time interval for requalification is six months. For grades C and D, the maximum time interval for requalification is 12 months.

The requalification gives the opportunity to critically evaluate the microbiological data. The microbial identifications are just as important during the requalification in order to assess changes and risk.

The draft Annex 1 also speaks extensively about the importance of trending data on a routine basis, not just during requalification. To adequately assess changes in flora type and numbers, there has to be complete confidence and reliability on the previously collected data. Frequent analysis of trends allows a proactive response to changes in the manufacturing environment. It helps identify controls to mitigate risk and protect the final product from contamination. It is not uncommon for regulatory inspectors to request trend reports and objective documentation for review.

TABLE 1

Recommended limits for microbial contamination in operation[1]

(Annex 1 draft, Table 2)

Grade	AIR SAMPLE cfu/m³	SETTLE PLATES (diam 90 mm),cfu/4 hours[(a)]	CONTACT PLATES (diam. 55mm), cfu/plate
A[(b)]	1	1	1
B	10	5	5
C	100	50	25
D	200	100	50

RECOMMENDED LIMITS FOR MICROBIAL CONTAMINATION IN OPERATION1 (ANNEX 1 DRAFT, TABLE 2.)

(B) IT SHOULD BE NOTED THAT FOR GRADE A THE EXPECTED RESULT SHOULD BE 0 CFU RECOVERED; ANY RECOVERY OF 1 CFU OR GREATER SHOULD RESULT IN AN INVESTIGATION.:

Risks of a failed cleanroom qualification

If the microbial identification method is inaccurate or irreproducible during the performance qualification, there is a false sense of control, additional time and money wasted to remediate contamination (both at the time of the qualification and in the future), ineffective action and alert limits, and delays in manufacturing. Those delays may cause drug shortages which would have a direct impact

TABLE 2

Recommended limits for microbial contamination[1]

(Annex 1 draft, Table 6)

Grade	AIR SAMPLE cfu/m³	SETTLE PLATES (diam 90 mm), cfu/4 hours[(a)]	CONTACT PLATES (diam. 55mm), cfu/plate	GLOVE PRINT 5 fingers on both hands cfu/glove
A[(b)]	1	1	1	1
B	10	5	5	5
C	100	50	25	—
D	200	100	50	—

(B) IT SHOULD BE NOTED THAT FOR GRADE A THE EXPECTED RESULT SHOULD BE 0 CFU RECOVERED; ANY RECOVERY OF 1 CFU OR GREATER SHOULD RESULT IN AN INVESTIGATION.

on patients and draw unwanted attention by regulatory bodies.

Since a new facility is under severe scrutiny by company executives, these undesirable outcomes can be very difficult to explain to management.

Outsourcing microbial identifications

Given the extent of the QC microbiologist's job functions and importance, as well as the importance of microbial identifications to the cleanroom's performance qualification, outsourcing identifications is a logical and beneficial option. Most commercial systems have limited throughput and cannot identify that large of a volume of microorganisms in a reasonable amount of time. All the data then must be compiled into a report and analyzed, which takes even more time and labor by the micro lab. Every day that it takes to complete the performance qualification means thousands of dollars in lost revenue.

The new Annex 1 draft also emphasizes the use of "scientifically sound and modern methods." This applies also to microbial identifications. Phenotypic systems that identify organisms based on biochemical and metabolic properties have been around for decades. The libraries associated with these systems are often limited and focused on clinical isolates. The identification rates can be subpar, and the number of retests requires more time, resources and cost. Identifications with phenotypic systems are less accurate and reproducible, especially as manufacturing isolates are stressed from the nutrient-poor environment and biochemical characteristics may not be expressed.

On the other hand, modern identification methods include genotypic DNA sequencing and proteotypic identifications using a MALDI-TOF mass spectrometer. DNA sequencing remains the "gold standard" for identifications, but typically requires more labor, more equipment, and technical expertise. Proteotypic identification methods do not offer phylogenetic information but are fast and reproducible. The MALDI-TOF

instrument is a significant investment, so many companies choose to outsource both DNA sequencing as well as MALDI-TOF identifications.

Considering that the importance of accurate and reliable microbial identifications is clearly emphasized for cleanroom qualifications in the Annex 1 draft, the optimal identification method is DNA sequencing.

When selecting an outsourcing lab partner, consider the availability of tracking and trending data tools. As mentioned in the previous section, Annex 1 expects frequent trending of environmental monitoring samples. Having trending organism reports included with the identification service could save significant time and reduce the risk of transcription errors. Thus, improving your data integrity position, and strengthening your compliance position. The trending reports can give a complete breakdown of what microorganisms were recovered from your cleanroom, allows you to easily view changes from your baseline, and assess remediation efforts.

Outsourcing your microbial identifications to a reputable company using robust and accurate services can give you confidence in your performance qualification. It can also speed up your timeline, allow you to make informed decisions about your process and contamination controls, decrease contamination risk, and save precious time and resources.

Another critical factor in selecting an outsourcing partner for microbial identifications should be appropriate lab accreditations such as ISO 17025. This accreditation certifies the technical competence of laboratories to perform specific tasks and guarantees that the results are obtained according to valid methods and procedures that comply with precise standards.

TABLE 3

Costs associated with a contamination event[2-6]

Issue	POTENTIAL IMPACT AND COST
Production interruption for alert	Up to USD 10,000
Commercial impact if cleanroom closed	Up to USD 1 billion in lost revenue ▪ Loss of reputation ▪ Drug shortages ▪ Lost business to competitors ▪ Fines
Failed production lot/scrap batch	Up to USD 1 million
QA investigation	Up to USD 60,000
Remediation of facility and equipment	Up to USD 100,000

*SEE REFERENCES FOR ESTIMATED FIGURES.

Worth the investment

The revised Annex 1 guideline places renewed emphasis on facilities and contamination control. This directly impacts cleanroom qualifications, which play a critical role in assessing the manufacturing state of control and establishing a baseline for assessing changes and risk to the final product. Accurate and reproducible microbial identifications in combination with meaningful tracking and trending of the generated results are necessary for effective contamination control and outsourcing these identifications can be beneficial.

Cleanroom qualifications are a huge investment of a company's money, time and resources. A strong and comprehensive qualification increases the company's regulatory compliance position, enhances product quality, and ensures patient safety.

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Thomas P. Wilson
Contract Manufacturing Lead, Pfizer CentreOne

High potency, high stakes

Exploring best-practice manufacturing strategies for highly potent oral solid dosage forms

As oral solid dose (OSD) drugs in development become more potent, regulatory expectations keep changing. To sustain compliance proactively, drug developers and their partners must develop a clear understanding to navigate current complex regulatory environments and build their manufacturing strategies accordingly.

Otherwise, you or your manufacturing partners might be at risk, blindsided during a facility inspection with a finding that not only will slow your drug's pace to market, but jeopardize its regulatory approval altogether.

Keeping up with market growth

Many people are relying on highly potent drugs to treat cancer, block immunological response to prevent organ rejection, provide contraception as well as manage a range of disease states and chronic conditions. The market is growing[1] and simultaneously has drawn increasing regulatory scrutiny. During processing and downstream manufacturing, exposure to these powerful drugs may be hazardous; to production personnel, to the surrounding environment and to patients via cross-contamination.

While regulators mandate protecting workers and preventing cross-contamination, historically they have never provided well-defined, harmonized standards for how to do it. It is up to manufacturers to determine how to meet regulators' expectations and demonstrate to regulators their methods are sufficient.

Various sources have created charts, lists and formulas for determining the risks posed by these drugs, along with a variety of recommendations for how to manufacture them safely. But without consistent guidelines, each pharmaceutical company has had to develop its own system for meeting regulator expectations. To make it even more challenging, the regulatory landscape has been shifting as the manufacturers have been responding to the development and growth of these potent compounds.

Regulatory models for manufacturing

Today, the regulatory environment is simultaneously governed by two main models: the "traditional" model, which has been in play for decades; and a newer, health-based model originated by the European Medicine's Agency (EMA). The health-based approach was adopted more recently by an international consortium of regulatory bodies, known as the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme or PIC/S — whose stated mission is to harmonize cGMP standards around the world.

Similarities

Notably, the traditional and health-based models possess striking similarities. Regarding implantation, each has effective, and each has less-effective methodologies to attain compliant containment. The absolute goal of containment is to protect workers and the environment from ambient, environmental exposure to the highly potent, highly active dusts and powders involved in the manufacturing process. This control is also necessary to help eliminate cross-contamination.

As a first line of defense, regulatory authorities prefer engineering controls — containing the compound within the manufacturing equipment so it doesn't escape into the work environment. Personal protection equipment, such as "bunny suits," provides supplementary protection.

To keep workers safe, plant operators periodically monitor the air employees breathe during the production process in order to ensure it meets acceptable exposure limits for the drug they are manufacturing.

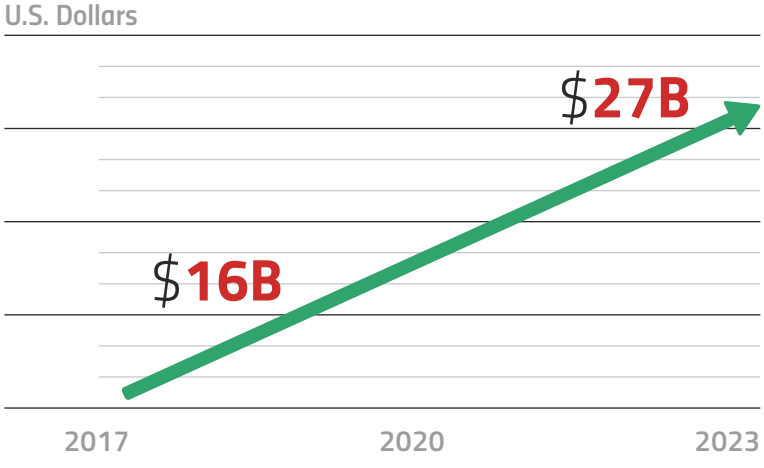
While various methods are used to determine these limits — commonly referred to as Occupational Exposure Limits (OELs) — they are mostly aligned and accepted within the traditional and health-based frameworks.

Differences

Where the two models diverge is their approach to segregation and cleaning validation, for example: With the traditional model, you segregate, and then you clean. With the health-based model, you clean, and if you can't clean well enough, you segregate.

EXHIBIT 1

Estimated growth of highly potent API market



Segregation refers to manufacturing drugs in separate facilities or self-contained areas. Originally, segregation was intended to prevent the cross-contamination of highly potent or highly active drugs, though that has largely changed due to advances in cross-contamination control.

Cleaning validation on the other hand provides cross-contamination control at the equipment level. Its goal is to protect patients taking the next drug made in the same equipment. After manufacturing a drug, you clean your equipment, and then you validate how well you've cleaned it. Operations technicians do this usually by assessing samples taken from inside the equipment and/or of the liquid used to rinse out manufacturing equipment after it's been cleaned. They can then identify if any remaining residue meets acceptable safety limits.

Traditional model: segregation then cleaning

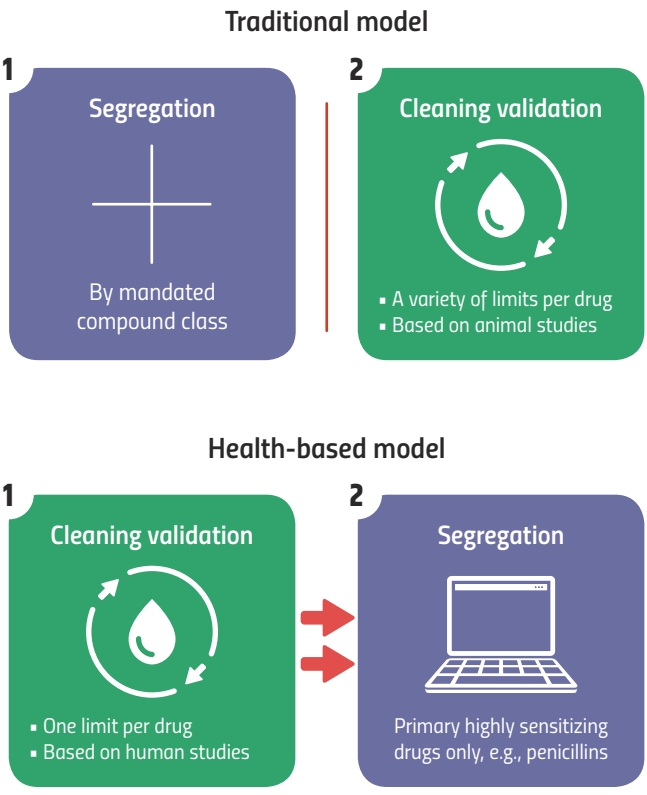
The traditional model mandates segregation by designated compound class, primarily to meet compliance for those countries that require it. You manufacture hormones in one facility or segregated area, immunosuppressants in another, sensitizers in another and so on. Everything else you can manufacture together in a general tableting or general solids area using your own cross-contamination control strategy.

When it is time to clean, it is time to meet safety limits per drug derived — primarily from animal toxicology studies. Operators can choose from a variety of generally accepted measurements, including toxicity thresholds (TTC) and lethal-dose limits (LD50s) based on rat studies.

Under the traditional model, segregation and cleaning validation are separate, unrelated activities.

EXHIBIT 2

Operational models



Segregation is segregation, and cleaning validation is cleaning validation.

Health-based model: cleaning then segregation

The health-based model takes an entirely different approach. Under this model, segregation is dictated by how well operators can control cross-contamination, with cleaning validation (which are based on different criteria) playing a pivotal role. Here, it is best practice to clean to meet a single safety limit per drug derived primarily from human safety data from clinical trials.

If you're able to meet that limit, you usually don't have to segregate: You've cleaned your equipment so well that whatever residue might remain will not contaminate the next drug made in that equipment or harm the patients who take that drug. If you cannot achieve the safety limit, you segregate.

Regardless of model, health-based or traditional, cleaning validation is only one part of a comprehensive cross-contamination control strategy. If you can't demonstrate contamination control for whatever reason, then it is time to segregate.

Currently, under the health-based model the only drugs that always need segregating, regardless of an organization's cleaning prowess, are highly sensitizing compounds

Pfizer Newbridge — Kildare, Ireland
To assure international compliance, Pfizer took a dual approach conforming infrastructure and processes to both the traditional and health-based models.

such as beta lactam antibiotics (i.e. penicillins). There is no acceptable exposure limit for these drugs because even imperceptible amounts may harm, or even kill people who are allergic.

Today's reality

How do you manufacture highly potent drugs compliantly in this complex and evolving environment? It's a challenge. While the industry is moving slowly toward the health-based model — more than 50 countries have formally signed on — the regulatory landscape remains in flux.

The reality on the ground is that inspectors who come to your facility may use either or both models to evaluate your operations: An inspector from a country that has accepted the health-based approach may still look for facilities segregated by traditional compound class. An inspector from a country using the traditional model may also want to see health-based elements in your manufacturing program. What's a manufacturer to do?

Pfizer's approach

Pfizer manufactures highly potent oral solid dosage forms at several facilities designed specifically for that capability. Given the regulatory scenario, Pfizer sought to create a safe, consistent and compliant approach to manufacturing that would serve Pfizer and Pfizer CentreOne's customers long term.

The Newbridge Ireland facility produces high-potency tablets, capsules and pellets. Since these medications are marketed in more than 100 countries, Pfizer needs to meet the scrutiny of inspectors from a number of jurisdictions, regardless of the regulatory model they use.

To assure international compliance at Newbridge, Pfizer took a dual approach conforming infrastructure and processes to both the traditional and health-based models. Because the company operates across the regulatory spectrum, as the industry moves in the health-based direction, Pfizer and its contract customers move along with it while continuing to meet contemporary expectations.

A plant-in-plant concept

Pfizer built the Newbridge plant to meet the segregation requirements of the traditional approach. The company's "plant-in-plant" design appears as one building from the outside, with a single roof covering almost a million square feet. However, lift off that roof and people will find 10 self-contained areas, each with its own air handling, material flow and personnel flow to achieve complete segregation.

The traditional model mandates segregation by specific compound class. Unfortunately, the point where to "slot" each compound varies among regulators around the world. At Newbridge, they use a Pfizer-proven process to classify each compound based on toxicological information derived from animal and human studies. The resulting classification dictates whether or not they should segregate.

For drugs that do not require segregation — and can be safely manufactured in a shared area — we conduct a formal quality risk assessment to make sure we have the technical and organizational controls in place to prevent cross-contamination.

This approach has served Pfizer well. As of this writing, the plant has been able to meet segregation requirements regardless of country throughout the facility's history.

Cleaning validation

As with segregation, Pfizer designed its cleaning validation criteria to satisfy both regulatory models. As a whole, traditional cleaning limits tend to be the more conservative, providing a wide margin of safety to allow for the indirect animal-to-human translation of study data. On the other hand, health-based cleaning limits are sometimes more generous: They're derived directly from human data so provide relatively fine-tuned margins of safety for human exposure.

Regulators, however, haven't loosened their requirements for cleaning levels, regardless of model. To satisfy the most stringent expectations,

we base our cleaning limits on both traditional and health-based calculations, and clean to the most conservative limit.

Containment

While getting segregation and cleaning validation right is critical, the most important health concern is safeguarding colleagues who handle these drugs every day. Even minimum exposure can have health consequences due to the potency of these compounds and frequency of contact.

To protect workers, the level of containment must be matched to a drug's risk. But no formula exists to make that determination. To provide a starting point for decision-making, Pfizer developed "Exposure Control Practices." Used across our global network, these procedures range from how to perform risk assessments to criteria for facility design, including room planning, air locks and exchange rates, and personal protective equipment.

While Pfizer provides criteria for equipment selection, facilities are not required to purchase specific models of tablet presses or fluid bed dryers, for example. At Newbridge, as at other Pfizer facilities, surveying the market and purchasing equipment that best matches the needs of projects and manufacturing environments maintains flexibility. This kind of flexibility enables Pfizer to stay current with technologies that are quickly evolving to better protect operators from exposure and control cross-contamination.

Finally, no amount of technology can safeguard the manufacturing environment without well-trained staff. Staff must understand how to handle these specialized compounds and systems — and themselves — with skill and compliance.

Keep up your commitment to compliance

As you manufacture highly potent compounds, in-house or through a CDMO, know that you need a manufacturing strategy that covers both the traditional and health-based regulatory models. Without it, you're taking a risk each time an inspector arrives at your door.

You need to keep up with containment requirements; it's not a static environment. Stay on the curve, if not ahead. And be committed. That's the hardest part of manufacturing! To stay in compliance, you need resources: the right people, enough time, and sufficient money to invest over the long term.

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Mark Quick
Executive Vice President of Corporate Development, Recipharm

The shifting CDMO landscape

Changes in customer demands and industry consolidation are creating new opportunities

Globally, the demand for pharmaceutical products has been steadily increasing as the world's population ages and the health care standards in developing countries rise. In response to market trends, the landscape for contract development and manufacturing organizations (CDMOs) is changing to meet evolving customer expectations.

The CDMO industry is currently a very fragmented space; the top five companies own less than a 15 percent share of the market. For the sake of comparison, in the contract research organization (CRO) market, the top five largest companies own 70 percent.[1] This is beginning to change however, as more mergers and acquisitions (M&A) take place across the CDMO sector, with significant consolidation expected in the next few years. This is in line with the preferences of many pharmaceutical companies. More and more customers are choosing to outsource to one full-service CDMO rather than several niche providers, as this simplifies the supply chain and can reduce time to market. In addition, to help bolster and expand their capabilities, many larger CDMOs are acquiring smaller, niche facilities in multiple locations, a trend we will see continue.

In terms of drug development, there is also greater demand for complex formulations. New technologies and development techniques are emerging, meaning controlled release and fixed dose combinations are becoming more achievable. Misuse and abuse deterrent technologies are also progressing, with novel solutions beginning to enter the market. These advances are likely to lead to greater patient adherence and safety.

This article will discuss emerging and continuing trends that the CDMO industry is likely to experience and how those in the outsourcing sector can be more prepared to meet shifting customer demands as the industry continues to evolve.

Supply chain partnerships

In recent years, the pharmaceutical market has experienced a lot of change, which has significantly impacted the CDMO sector and demand for its services. With the pharma industry worth $1.2 trillion in 2018, IQVIA predicts that it will be worth over $1.5 trillion by 2023.[2]

Many pharmaceutical companies are seeking advanced supply chain opportunities in order to optimize the development of their molecule. The integration of multiple facilities gives CDMOs access to specialized technologies, expertise and additional resources, which ultimately strengthens their scope of capabilities. As such, they have the capacity to deliver streamlined, end-to-end development and manufacturing offerings to customers, and produce marketable products within a quicker timeframe. This has led to a lot of firms establishing a partnership with a CDMO as opposed to investing internally on infrastructure.

Consolidation trends

Another key trend in the outsourcing sector is the proliferation of M&A strategies. Research has found that M&A activity has been accelerating since 2012, increasing approximately 12 percent each year.[3] As such, we are likely to see more consolidation of CDMOs throughout 2019 in order to facilitate supply chain efficiencies, improve lead times, expand geographical reach and advance capabilities.

Industry consolidation has been partly driven by the desire to diversify capabilities, so that CDMOs can effectively provide customers with comprehensive end-to-end drug development and manufacturing services, whilst also reducing operational costs. This is because drug developers are keen to progress their drug product to market as quickly as possible, with minimal supply chain complexity. Additionally, changing service providers mid-development incurs heavy expenditure and so full-service providers are often seen as way to decrease overall costs for drug developers.

Another factor impacting the proliferation of M&A strategies is the current fragmented state of the sector. As manufacturing activity continues to be actively outsourced, companies are consolidating in a bid to meet customer demand and maintain a successful position within the sector. In acquiring new technologies and capabilities, contract service providers can streamline their overall service spanning drug development to commercial product.

M&A activity has been increasing since 2012 by about 12 percent each year.

New markets

By acquiring new facilities, companies can expand their global presence and reach new markets.

Although there are many opportunities available within the European market, it does present some challenges such as the need to cater for a diverse range of packaging variations as a result of varying legislation and the vast amount of languages spoken across the continent. In contrast, the U.S. provides many operational and market benefits. For example, the U.S. landscape offers companies a common language and legislative requirements for around 300 million citizens, which ultimately lessens the likelihood of experiencing any logistical issues. Outsourcing to a CDMO with experience and a presence in both markets can help to manage this complexity.

An emerging market that is increasingly sought after is India. This is because it has a reputably skilled workforce and can offer companies more cost efficiency as opposed to western countries. Moreover, India has secured 34 percent of all Abbreviated New Drug Applications (ANDAs) and received a total 1,842 ANDA final approvals by U.S. Food and Drug Administration (FDA) in the period between 2009 to 2018,which further solidifies its position as a strong market. CDMOs are already starting to build their presence in this growing market and this trend is expected to continue.

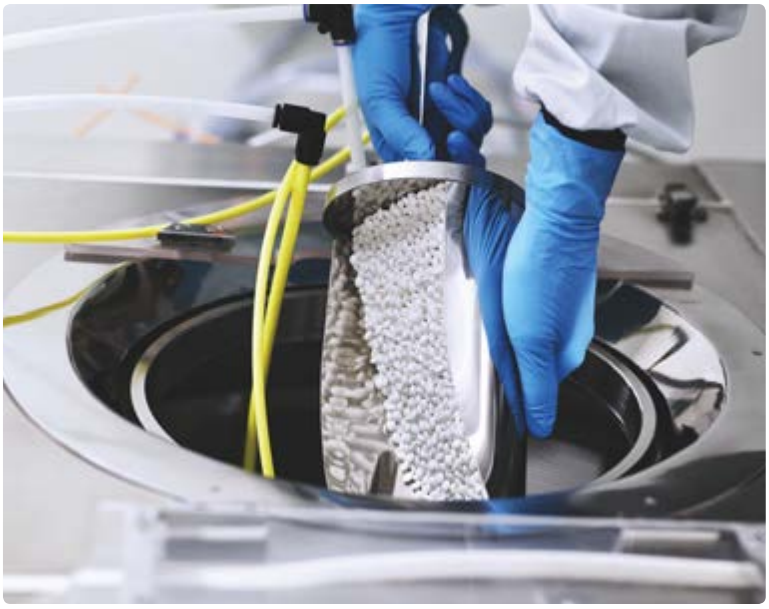
Drug development trends

A primary drug development trend is the use of the 505(b)(2) new drug applications (NDA) pathway. It is growing in popularity amongst pharmaceutical drug manufacturers due to the efficient route to market it offers new drugs as a result of

Photography courtesy of Recipharm

companies being able to reuse existing data for well-understood APIs. The 505(b)(2) pathway has sparked an interest in the development techniques available for orally inhaled products and nasal sprays, such as spray drying. Thus, it is expected that demand for inhalation services will increase as drug developers explore efficient delivery routes to facilitate enhanced therapeutic effects for patients.

In addition, following the increasing concerns around prescription drug abuse, global regulators have recommended that drug developers ensure that certain products contain technologies in order to minimize abuse, particularly those including opioids.[4] This notion has impacted formulation development as it has encouraged pharmaceutical companies to develop technologies that will prevent the API being released through drug product manipulation.



How to prepare

Of course, in a shifting regulatory environment with evolving customer demands, CDMOs must always be thinking about what is next. A recent case in point was the enforcement of the EU Falsified Medicines Directive (FMD) regulation in February 2019. The development and implementation of solutions to meet serialization requirements caused operational upheaval across the sector. Designed to protect the security and legitimacy of pharmaceutical products circulated in the European market, the new legislation called for redefined supply chain processes that would meet the FMD regulations. This proved to be a complex procedure. As uncertainties surround the future of serialization, companies must actively seek opportunities to futureproof their offerings in order to effectively respond to the evolving legal landscape of multiple markets.

Pharmaceutical firms should also seek to invest in their sustainability efforts in order to maintain compliance and be prepared for tightening requirements in the future.

Going forward, the emergence of precision medication will require CDMOs to adjust their manufacturing strategies and processes. As such, contract service providers will need to be able to potentially distribute smaller and personalized batches alongside larger volumes. CDMOs can prepare for these new drug pipeline requirements by adapting and ensuring they are agile and flexible in their approach. Flexibility and agility are already sought-after attributes of a modern CDMO. By establishing processes that can be scaled up or down to meet the volume requirements for new chemical entities (NCEs) and ensuring a breadth of technologies and capabilities are available CDMOs can start to futureproof their offering. These assets complement existing management capabilities, enabling CDMOs to offer customers integrated services, refine deliverables, speed up timelines and ultimately develop drug products at a quicker pace.

As the CDMO market continues to evolve, pharmaceutical companies will be exposed to new opportunities and demands throughout the year. Both consolidation and the emergence of new technologies are enabling companies to innovate new and existing drugs, while also improving the customer experience, reducing timelines and costs.

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Reducing the burden

How new formulations can improve solubility and lower the pill burden of kinase inhibitors

Small molecule kinase inhibitors are a class of drugs used in the treatment of cancer and autoimmune diseases. The U.S. Food & Drug Administration has approved more than 45 kinase inhibitors since they first reached the market in 2001 with Gleevec. The total revenue generated by kinase inhibitor drug products worldwide now exceeds $30 billion per year.[1] With seven approvals in 2017 and eight in 2018, and more than 250 currently in development, it appears the number of kinase inhibitor therapies will only increase in the coming years.

Despite their abundance in cancer therapy, kinase inhibitor drugs are often plagued by challenging physicochemical and biopharmaceutical properties, including high dose, low water solubility and high lipophilicity, which can lead to unoptimized absorption and pharmacokinetic properties. When uncorrected by an enabling formulation approach, poor drug absorption can result in a high pill burden, food-label restrictions and absorption-related drug-drug interactions in patients. The net effects of these dosing and pharmacokinetic issues are reduced patient compliance and inferior therapeutic outcomes.[2,3] Yet only three of the 45 FDA-approved kinase inhibitor products utilize an enabling formulation approach, in part because the treatments are often fast-tracked to the market, which can limit scope to explore alternative formulation approaches to optimize absorption. Also, kinase inhibitors are frequently hard to develop using two common enabling formulation techniques — spray-dried dispersions and lipid-based formulations.

> Drug developers and patients may benefit from exploring formulations that use the lipophilic salt form of kinase inhibitors, which can improve solubility while lowering product pill burden. The lipophilic salt approach can be easily scalable and presents opportunity to use the 505(b)(2) regulatory pathway for accelerated development of approved drug products, helping reach patients sooner with a drug product that is optimized for absorption.

Need for innovative formulations

Two of the most commonly used enabling formulation techniques the pharma industry currently uses to solve the downstream problems associated with low drug solubility in water and high drug lipophilicity are amorphous spray dried dispersions (SDD) and lipid-based formulations (LBFs).[4] SDDs consist of amorphous drugs within a polymer matrix, improving drug absorption by eliminating crystalline barriers to low drug solubility. They can be delivered to the patient in the form of a tablet or powder in capsule finished dosage form. Drugs that are typically well suited to the SDD approach are those that show "brick dust" type properties, showing a high melting point and low solubility in aqueous and non-aqueous solvents.

LBFs consist of drug either suspended or dissolved within a vehicle consisting of oils, surfactants and/or cosolvents and delivered via two-piece hard capsules or soft gelatin capsules. Improved drug solubility along the GI tract improves drug absorption for LBFs, while those LBFs containing dissolved drug typically show higher absorption and reduced variability in vivo as they also eliminate crystalline barriers to low drug solubility. LBFs tend to be appropriate for drugs that show "grease ball" properties, showing low solubility in water but high solubility in non-aqueous solvents such as oils.

EXHIBIT 1

Dissolving the highest clinical erlotinib dose (150 mg) in a model lipid-based formulation

HCl salt
~90 g lipid formulation to dissolve 164 mg HCl salt (110 x size 00 capsules)

Free base
~7.5 g lipid formulation to dissolve 150 mg of free base (10 x size 00 capsules)

Lipophilic salt
~0.45 g LBF to dissolve 309 mg of lipophilic salt (1 x size 00 capsule)

Kinase inhibitors are often not ideal for either SDD or LBF, as they frequently show intermediate brick dust/greaseball properties. This can lead to high pill burden, lower patient adherence and undesirable treatment outcomes. For example, erlotinib, currently marketed as Tarceva and FDA approved in 2004 for the treatment of metastatic non-small cell lung cancer and advanced-stage pancreatic cancer. Erlotinib would initially be considered a good candidate drug for an enabling technology approach owing to its low aqueous solubility in the small intestine (its primary site of absorption), low and variable absorption in the fasted state and clinically significant enhanced absorption when taken with food.[5] However, erlotinib shows very low solubility in lipid vehicles. The LBF volume to deliver the target clinical dose translates to more than 100 regular sized capsules when using the marketed salt form (hydrochloride) (see above). When using the free base form of the drug, the situation is improved but 10 capsules are still needed for a single dose. This number of capsules is impractical for the patient, even in the treatment of cancer.

Lipophilic salt forms — new tricks

Transforming a kinase inhibitor into lipophilic salt form is one promising approach for improving the solubility of kinase inhibitors in LBF vehicles so these drugs can access the benefits of LBF without a high pill burden.[6,7,8] The conversion of drugs into salts in drug development is not new, as salts have been used for decades to improve the manufacturability of drugs and increase drug solubility in water.[4] However, lipophilic salt forms are different in that they are specifically designed to show improved solubility in lipid-based vehicles. The net effect is that lower volumes of LBF are required to deliver the target dose. Revisiting the erlotinib example above, using the lipophilic salt form of this drug has made it possible to deliver the maximum dose in one capsule — rather than 100.

While the lipophilic salt form takes care of the pill burden, the LBF vehicle itself takes care of the kinase inhibitor's low solubility in water. This has been proven both in laboratory tests as well as in in vivo tests where it has been shown the LBF and lipophilic salt form work "synergistically" to increase the amount of drug dissolved in simulated intestinal conditions, which in turn translates to increased drug absorption.[8] The combined use of lipophilic salts of kinase inhibitors and LBF is therefore a new approach available to chemists and formulators working in this area.

Notably, the lipophilic salt will not change the way in which the kinase inhibitor works after it is absorbed. This is because lipophilic salt formation does not involve a change in the covalent drug structure — the kinase inhibitor and the lipophilic counterion will dissociate before it crosses the intestinal membrane or before it reaches the bloodstream. The benefit of this is that lipophilic salt forms are not new chemical entities (NCEs) in the regulatory sense, meaning that existing safety and pharmacology data relating to the kinase inhibitor can be leveraged during submission. As the synthesis of lipophilic salts is, once optimized, generally high yielding and operationally simple, the approach is readily scalable for clinical development through to commercial supply.

Looking ahead

The lipophilic salt approach brings a new opportunity to chemists and formulators to deliver new kinase inhibitors currently under development in an optimized finished formulation, with reduced risk of high pill burden and absorption-related issues such as variability and food-effects. As the approach piggy-backs existing synthetic infrastructure and is combined with the well-known formulation platforms, it is readily scalable, meaning it can be pursued in new kinase inhibitor development projects that are likely to be or already are on fast-track status. Another potential benefit is that new drug applications relating to new salt forms and new formulations of FDA approved kinase inhibitors could all be filed via the 505(b)(2) pathway, which has the benefit of shorter development times and up to five years of exclusivity.

Kinase inhibitor drugs offer promise for advancing novel cancer treatments, but their low solubility can lead to challenges in terms of pill burden and adverse outcomes for patients. Common techniques for bioavailability enhancement, such as spray-dried dispersions and lipid-based formulations, are not ideal for many kinase inhibitors due to their physicochemical properties. Transforming them into their lipophilic salt form can allow the use of lipid-based formulations to increase bioavailability and lower pill burden.

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product focus

Meagan Parrish
Senior Editor

Optimizing your ebb and flow

New approaches to fluid control enhance pharma manufacturing

It's no secret that in pharma, consistency is king. When it comes to fluid handling, manufacturers need components that will churn out reliable and safe results. But there are also opportunities to maximize this critical area of operations to boost speed, increase efficiency and control costs.

As pharma companies look for ways to optimize fluid handling, vendors have stepped up to innovate solutions to help them achieve better results.

Saint-Gobain's ValPlus family of products provides a higher level of quality assurance.

Continuous processing

For years, pharma companies have been looking for more ways to transition parts of their operations into continuous manufacturing, and that trend is showing no signs of abating. Switching to continuous processing provides several key benefits to manufacturers.

"Traditionally, virtually all big pharma manufacturing operations have used the tried and tested batch approach to meet regulatory requirements for good manufacturing practice (GMP)," says Jim Sanford, senior product manager of Fluid Paths at Watson-Marlow. "However, continuous processing has the potential to improve efficiency by decreasing processing times, eliminating unnecessary steps and streamlining the entire process, as well as increasing drug quality by reducing batch-to-batch variability. As a result, we are seeing growing demand for certified solutions for continuous processing."

With that goal in mind, Watson-Marlow has developed a range of fluid components the company says can be easily assembled into a complete manufacturing processes for end-to-end fluid management.

"For example, our BioPure range offers FDA-compliant gaskets and connectors in a range of materials to satisfy GMP requirements and facilitate process validation," Sanford explains.

The company's BioPure gasket range was developed with materials such as polytetrafluoroethylene, a synthetic rubber and fluoropolymer elastomer to ensure chemical and steam resistance. The components also support leak resistant connectivity within pharmaceutical and biotechnology production processes, which reduces validation risks in contamination-free applications.

"The new range of materials offered will provide our customers with

greater choice to design fluid paths that satisfy their production needs," says Mark Lovallo, product manager of Watson-Marlow.

Safeguarding cells

As pharma companies look for ways to boost efficiency, there has also been an increased emphasis on improving cell viability.

"The demand for greater production efficiency is driving manufacturers to maximize cell viability throughout their processes," says Phil Nyren, product manager, Fluid Handling, Cole-Parmer.

According to Nyren, companies are specifically looking for ways to reduce the amount of shear in fluid systems, which can be accomplished in a few ways.

"The first option is to decrease the speed of the pump to reduce the damaging forces placed on the cell suspension. Flow rates can be maintained at reduced speed by increasing the tube diameter in the fluid system. Another way is to specify a pump with low-shear characteristics," Nyren says.

To that end, Masterflex Cytoflow pump systems by Cole-Parmer feature convex rollers with a concave occlusion surface that limits shear as the tubing is progressively occluded. The company says that the introduction of convex rollers in Masterflex peristaltic pumps has also improved performance in applications involving live cells and other shear-sensitive fluids.

Cole-Parmer's Masterflex peristaltic pumps have improved performance in applications involving live cells and other shear-sensitive fluids.

Contamination control

The integration of single-use components also continues to be an effective way for manufacturers to limit contamination risks.

"As this trend continues to develop, pharmaceutical manufacturers are requesting single-use system manufacturers to provide assurance that their single-use products are in compliance with current good manufacturing practices and do not alter the drug products beyond established regulatory requirements," explains Aaron Updegrove, marketing director of Bioprocess Solutions at Saint-Gobain.

But according to Updegrove, tubing products are still rarely certified to meet endotoxin, bioburden and particulate standards.

"In some cases, pharmaceutical manufacturers have taken their own risk mitigation measures to reduce potential contamination such as rinsing tubing products with water for injection. However, these strategies are costly and in some cases, infeasible," Updegrove explains.

Updegrove says that Saint-Gobain Life Sciences' ValPlus products provide pharma manufacturers with an enhanced level of tubing certification and confidence in the cleanliness of the tubing products they use in critical applications. This enhanced documentation is available for a variety of Saint-Gobain tubing brands including C-Flex and Sani-Tech, and provides certification to USP <788> for particulate, USP <85> for bacterial endotoxin, and ISO 11737 for bacterial and fungal bioburden.

"This higher level of quality assurance is an industry-leading effort to quantify and reduce risks associated with fluid path contamination," Updegrove says.

Ultimately, vendors are showing that manufacturers can find plenty of pathways to reducing costs and improving efficiency in their tubing and fluid control systems.

Saint-Gobain's ValPlus products are available with an enhanced level of validation documentation.

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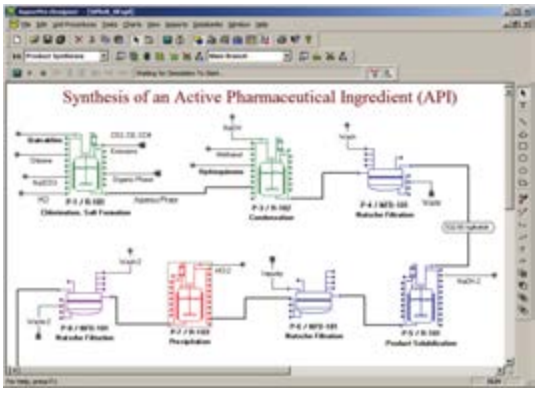

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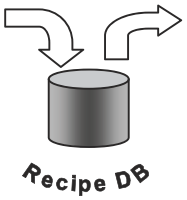

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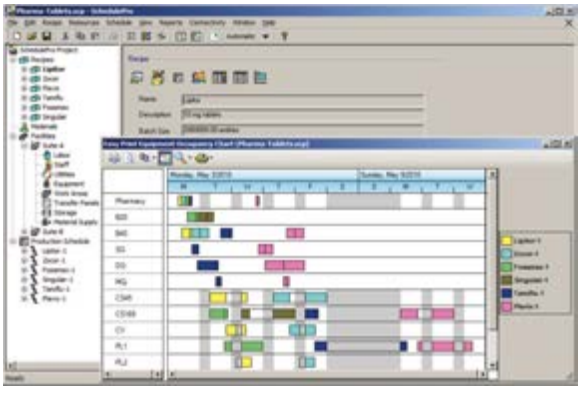

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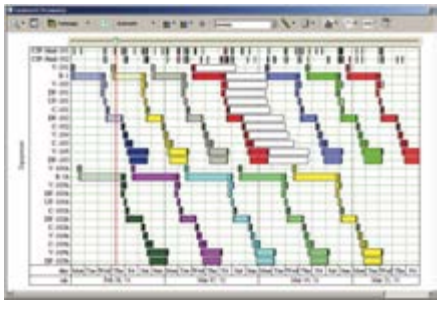

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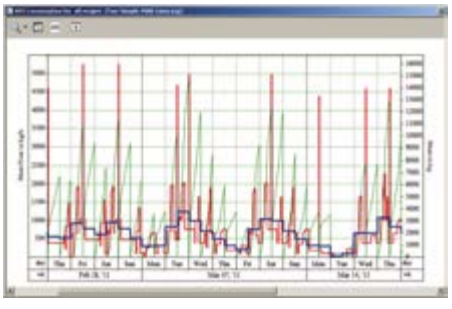

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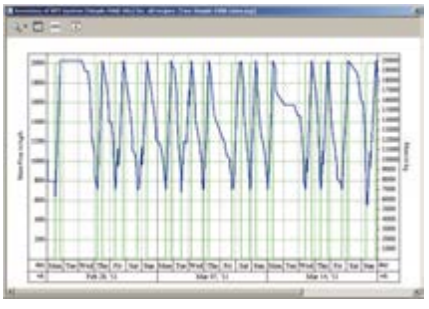

Managing inventories for input, intermediate, and output materials

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of integrated biochemical, bio-fuel, fine chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 500 companies and 900 universities around the globe (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

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

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Data analytics moves beyond Dilbert

Why you shouldn't get stuck in a comic

Until recently, data analytics has been in a realm of manufacturing only occupied by the mysterious engineers who graced the colorful squares of Dilbert comics. A world where management is clueless, timelines are open-ended, the engineering department is an impenetrable black box and IT resists all change. While it can be frustrating to work in a corporate structure where the value of data isn't recognized, or where technology solutions may not be properly funded, there is hope.

In modern manufacturing, data collection and analysis are the keys to the kingdom, and the technology is available to unlock business value. Understandably, deciding to invest even more money, time and resources into the world of big data can be daunting. However, when a passion for creating real change in an organization combines with data analytics technology, therein lies great opportunity for impact.

Painting a picture for decision makers that clearly shows what success looks like is imperative. Hesitation to act, due to either technical reasons or personal fear of failure, can hinder taking the steps required to effect change. However, with a clear vision, strategy and shift in cultural values, it is possible to establish and execute a winning business case for investment in advanced analytics. This requires showing everyone involved what's in it for them, and how investments will deliver measurable success.

In my experience, the most frustrating, destructive and unfortunately, pervasive attitude is that there is no time for change, but there is plenty of time to slog away in complex spreadsheets that don't provide insights quickly and hinder the ability to share findings effectively. Instead, we must be clever and employ an agile approach with phases that support early wins. These phases are discovery and launch, extended engagement and strategic alignment.

In the discovery and launch phase, business initiatives and key performance indicators are identified. Workflows are redefined as required with an understanding of desired short-term outcomes, and a shared set of terms is created to ensure broad understanding while avoiding unnecessary jargon. This first step can be difficult and is often met with significant resistance.

Overcoming this inertia requires one to:

- Align data capture strategy, process analytical technology and analytics goals.
- Empower Subject Matter Experts (SMEs) with advanced analytics tools designed to work with process manufacturing data. Technologies that couple the intuition and experiences of SMEs with the power of machine learning will provide the greatest impact.
- Remove technology and workflow barriers to facilitate access to a data-rich environment for individuals and teams.

In the extended engagement phase, a successful strategy will target opportunities to unite teams.

Since departments are often mired down in their own protocols, it is important to:

- Provide clear demonstration of how the strategy and advanced analytics solution benefits groups working together.
- Define actions required to shape and encourage a culture of engagement and risk-taking.
- Identify leaders who can help drive these cultural shifts.

In the strategic alignment phase, it is time to solidify the commitment to the broader digital transformation strategy. Having employed an agile approach, the early results should have quickly demonstrated value.

This phase focuses on securing the additional emotional and financial investments required to further drive growth and profitability by:

- Identifying new value-added workflows.
- Evaluating new opportunities for cross-site decision making.
- Asking and answering more strategic, complex and high-level business questions.

Instead of remaining stuck in the middle of a Dilbert comic, why not spend time and energy driving towards a winning business case for investment in advanced analytics? Embrace the risk. Extract the value. Savor the results.

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