American Pharmaceutical Review

The Review of American Pharmaceutical Business & Technology

Volume 25 Issue 7 | November/December 2022

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American Pharmaceutical Review™

COVER FEATURES

IN THIS ISSUE »

It's Easy To See

BET Sustainability

LAL Reagent Comparison Table	Conventional LAL Reagent	**ACC's PyroSmart NextGen® (rCR) Reagent**	First Generation Competitor (rFC) Reagent
Sustainable Reagent (animal free)	**No**	✓ **Horseshoe Crab Blood Free**	✓ **Horseshoe Crab Blood Free**
Kinetic Assay	Kinetic	✓ Kinetic	✗ **No.** Endpoint only
Assay Setup	Single step reconstitution	✓ Single step reconstitution	✗ **No.** rFC requires three reagents in a 1:4:5 ratio and a 10 min. pre-incubation step
Same Standard Plate Reader	Incubating plate or tube reader at 405 nm	✓ **Yes.** Incubating plate or tube reader at 405 nm	✗ **No.** Fluorescent reader required
Derived From *Limulus* Amebocyte Lysate (LAL)	LAL	✓ **Yes.** rCR is recombinant LAL	✗ **No.** Based on *Carcinoscorpius* or *Tachypleus* Amebocyte Lysate (CAL/TAL)
Multi-step Cascade Pathway	Yes	✓ **Yes**	✗ **No**
Endotoxin Specific	No	✓ Endotoxin Specific	✓ Endotoxin Specific

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Message from the Editor

Brain Surfing

Much like surfing the web, my thoughts typically lead me from one topic to another, like clicking on links in an article. Sometimes I end up in places I would never have predicted. But it is amusing.

As part of our holiday tradition, we kick-off the season by watching the movie, Elf. While the movie is ostensibly about Will Ferrell's Buddy the Elf character, it is also about James Caan's character. Walter Hobbs is a publisher of children's books, and makes the transformation from a grouchy, Grinch-like person, into someone who believes in Santa Claus and embraces the Christmas Spirit.

I was saddened watching the movie this time, as James Caan passed away earlier this year. I started thinking about his movie career – how he had always played tough guys, and the role of Walter Hobbs was quite a departure for him – but probably one of his best-loved characters.

Thinking about Caan's other roles reminded me of his movie Thief described by Wikipedia as a: "1981 American neo-noir heist action thriller film directed and written by Michael Mann in his feature film debut. Based on the 1975 novel The Home Invaders: Confessions of a Cat Burglar by Frank Hohimer, the film stars James Caan in the title role, a professional safecracker trying to escape his life of crime, and Tuesday Weld as his wife. The supporting cast includes James Belushi, Robert Prosky, Dennis Farina, and Willie Nelson. The original musical score was composed and performed by Tangerine Dream, with additional music composed by Craig Safan."

If you haven't seen it, I highly recommend it.

Thinking of Thief got me thinking about Theranos, as the CEO was just sentenced to prison. According to one source investors lost $600M on what was essentially non-existent technology. All investing involves risk, but I think this goes beyond that. This was thievery.

But let's get back to Elf for a minute.

In an early scene Walter Hobbs is confronted by his boss about a book that is missing the last two pages. Hobbs tries to blame it on a printer error, but his boss has the page proof with his initials approving the blank pages.

As an editor I always wondered how someone could intentionally do something like that, or, just miss the fact that something was missing.

Well, in the October/November issue it happened. The final page of an article went missing. I'm not sure how it happened, but I missed it. As the editor, it's my fault.

The article in question is Implementing Process Improvement by Robert Dream.

Bob has been a frequent contributor to APR over the years and upon receiving his email asking what happened to the last page of his article, I immediately felt a pit form in my stomach. Upon further investigation, sure enough, it was missing.

To Bob, I apologize for the mistake. The complete article is posted on APR's website and is correct in the digital edition.

Have a great holiday season!

Mike Auerbach
Editor-In-Chief
mauerbach@comparenetworks.com

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CNPerspectives

CompareNetworks

American Pharmaceutical Review is one of several outstanding publications available from CompareNetworks, Inc. Here is a look at the insightful content our readers may enjoy from four of our sister resources: *Pharmaceutical Outsourcing*, Biocompare, Labcompare, and *Tablets & Capsules*.

Best Practices for Data Collection in Decentralized Clinical Trials

Pharmaceutical Outsourcing™

Over the past few years, impactful technology advancements have been made in the clinical trial industry that have resulted in better opportunities to conduct decentralized clinical trials (DCT). COVID-19 further propelled the need for implementation of DCTs and the ability to collect data outside of the traditional site-focused model.

There are now tools available within the industry to implement DCTs quickly and effectively. With proper application, impressive strides can be made to improve the site and patient experience, provide opportunities for data to be collected directly from patients, and, in turn, reduce some of the challenges of collecting quality and real-time data.

https://bit.ly/3XDQoNv

A Guide to Hematopoietic Stem Cell Markers

Biocompare

Blood cells are rather short-lived and thus require continuous replenishment. This need is met by hematopoietic stem cells (HSCs), which are rare (0.005%–0.01% of all nucleated bone marrow cells), self-renewing cells that through a series of lineage-committed progenitor cells ultimately give rise to mature blood cells of all types. Their therapeutic potential for treating hematological disorders is immense, but a shortage of immunocompatible HSC donors means that generating a sufficient number of transplantable HSCs is a sought-after achievement in clinical research. Preclinical research into developing methods to maintain, manipulate, and expand HSCs ex vivo is paving the way to making widespread clinical usage of HSCs a reality. Their isolation for such studies is based on the expression of a distinct pattern of cell surface markers well reported in the primary literature, which will be discussed in this article.

https://bit.ly/3GXFSed

Advances in Whole Slide Scanning: Where the Technology Is Today

labcompare

Whole slide scanning has emerged as an invaluable tool in a range of research and clinical applications in recent years. Given the large areas that must be covered, typical approaches involve scanning slides at low magnification (10x–20x) and have been limited in application to the detection and analysis of objects resolvable at these magnifications.

Recently, numerous improvements have been made that make high-resolution slide scanning possible. However, several tradeoffs exist when considering low- versus high-resolution scanning. In comparison, low-resolution imaging—here defined as images collected at 2x–20x magnification—provides high acquisition rates (especially for large area samples) and a macro-scale overview of features or structures, while keeping file sizes small and data volumes manageable.

https://bit.ly/3ANL5RK

Tamping: Fine-Tuning Capsule Filling

Tablets&Capsules

If you're thinking about encapsulating high-volume, well- formulated products, a tamper-style encapsulator is your best bet (dosator-style encapsulators work with sticky products, while hand-filling-style machines handle coarse products and small volumes well) Tamper-style encapsulators use pins to push through a pile of powder, forcing an ambiguous amount into a dosing bore. This is repeated several times prior to transfer into the capsule body.

The capsule's contents is called a "slug". An ideal slug is cylindrical, semi-solid, uniform, and flat on top and bottom. A consistent slug promotes accurate fill weight and clean transfer into the capsule body at high speeds.

https://bit.ly/3i9xQUY

Social Media Connections

U.S. FDA
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#DYK African American and Hispanic/Latino populations are disproportionately affected by #Alzheimers? Learn more about the symptoms and risk factors via @FDAHealthEquity https://ow.ly/o3uS50LwrX2 #AlzheimersAwarenessMonth

BioNTech SE
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We published new data on the immune response induced by our Omicron BA.4/BA.5-adapted bivalent #COVID19 vaccine against newer Omicron sublineages, incl. BA.4.6, BA.2.75.2, BQ.1.1 & XBB.1. https://investors.biontech.de/news-releases/news-release-details/pfizer-and-biontech-report-new-data-omicron-ba4ba5-adapted

U.S. Pharmacopeia
@USPharmacopeia

Obstacles manufacturers can face when considering adoption of pharmaceutical continuous manufacturing include workforce capacity challenges, lack of clarity on return-on-investment, regulatory uncertainties, and internal resistance to change. Learn more. https://bit.ly/3tn1UyV

Pfizer Inc.
@pfizer

A common misconception you may see on the Internet is that #COVID19 vaccines and treatments for COVID-19 are one in the same – the truth is that they serve different purposes. Our scientist friend Darrion breaks down the difference between COVID-19 vaccines and treatments. https://twitter.com/i/status/1595139236402954241

PhRMA
@PhRMA

The need for new antimicrobials has never been greater — with drug-resistant infections on the rise amid #COVID19. Six of the 18 most alarming AMR threats cost the U.S. more than $4.6 billion annually, and the PASTEUR Act can help. http://bit.ly/3tzCPkh

EU Medicines Agency
@EMA_News

Are you a #ClinicalTrial sponsor? As of 31 January 2023, you will have to use the Clinical Trials Information System and follow the same process to apply for the authorisation of a clinical trial in the #EEA.

American Association of Pharmaceutical Scientists
@AAPSComms

Time is running out to #volunteer. AAPS seeks experienced scientists like you to lead the NBC Abstract Screening Committee. This Committee selects the poster abstracts that will bring novel science to the National Biotechnology Conference (#NBC2023).

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For clinical researcher Janethe Pena, unmet needs in patient health serve as an urgent call to action. Learn about her work in pulmonary arterial hypertension: merck.us/3zuZuBJ #PHAwarenessMonth

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The Fractured Landscape for Pharmaceutical Manufacturing Education

How a fractured training and upskilling landscape feeds continuing pharma quality and compliance issues

Michael I. Levitt

Vice President, Strategic Operations
Quality Executive Partners

If you are like me, you receive a dozen or more invitations to webinars, seminars, and conferences every day. Each invitation promises to provide insight into a host of critical issues impeding success in the world of pharmaceutical/biotech development and manufacturing.

A colleague recently pointed out that despite the overwhelming number of offerings, cleaning validation 483 observations from the FDA, (these indicate practices that may compromise cleanliness or result in microbial or chemical contamination), increased almost 70% in the last ten years over the previous decade. And while we can debate the causes; this apparent performance decline is not an isolated problem.

We belong to an industry focused on the health and wellness of people. It is imperative that we challenge ourselves to get to the root cause of what is impeding our ability to execute regulations which were put in place to ensure safe and effective product manufacturing. Why has industry performance declined over the last two decades?

Regulatory Oversight and Enforcement is Not the Solution

Despite the best efforts of global regulators, over the last 110 years, the process of achieving quality compliance by enforcement action has not been successful.

The rapidly changing dynamics of our industry mirrors a revolution in the development of miraculous products in biopharmaceuticals,

biosimilars, as well as cell and gene therapies. Concurrently, we face the challenges of engaging new strategic and tactical approaches such as outsourcing a significant percentage of manufacturing to third parties. These evolving strategies demand a higher level of decision-making acumen and critical thinking skills to ensure the quality of what the public receives.

The Training and Education Gap is Growing

All of us working in this industry consider ourselves to be experts; but how does our preparation compare to other groups of professionals? In the pharmaceutical industry, training remains focused on developing the individual's ability to properly execute a discrete task. This focus is a vestige of 19th century norms and schema. We develop skills through apprenticeship – work with more experienced experts who then teach skills in return for the apprentice's labor.

The explosive growth of biopharmaceuticals and advanced therapies has brought with it the possibility of a world changing future for personalized medicine and disease treatment. However, this same mind-blowing opportunity has also created a massive gap between existing and needed talent. Our industry may face a catastrophic shortage of workers who possess the skills needed for advanced therapy manufacturing.

Further compromising the existing training model is that these rapidly developing technologies result in a lack of skilled or experienced leaders/mentors to teach new workers. The lack of these leader/mentors is exacerbated in this space because technicians' manipulations require not only the physical capability to execute the process but the ability to make critical decisions when issues are encountered. Any new learning and development frameworks must engage the metacognitive, kinesthetic, and academic specifics which are unique to these novel manufacturing methodologies. We must devise teaching and learning structures which deal with the short and long term needs of the industry.

The industry is responding to these needs by creating innovative, pliable, tech-forward training and education tools which include immersive simulation based, virtual and augmented reality. The best of these tools includes both education in the concepts underlying the process and the ability to practice in a risk-free environment. This shift is proving effective in training the technicians who execute the work because of the inherent, learner centered benefits of these personalized learning platforms

Some early efforts which utilize automation and artificial intelligence are also focusing on the gap at the worker level. What remains, however, is a huge gap in the expertise of the leaders and experts who design and maintain the processes, equipment and facilities needed to meet complex global regulatory requirements. Those charged with ensuring that the products produced consistently meet the standards for safety, purity, and effectiveness.

Regulations Can Only Do So Much

The European Union has attempted to address the variability we see in the interpretation of quality compliance regulations with a legally mandated requirement for a "Qualified Person (QP)" who meet specific educational and experience requirements as defined in "Directive 2001/8/EC of the European parliament and of the council of 6 November 2001 on the community code relating to medicinal products for human use."

This approach has its limitations in that it provides a legally required retrospective review of product performance prior to release. In the rapidly growing areas of advanced therapies and biopharmaceuticals, the QP can prevent release of compromised materials but cannot ensure consistent and sustainable performance. It requires a different skill set to take the feedback from the QP and apply it prospectively as a process improvement, risk reduction, or preemptive measure.

In the United States, the Code of Federal Regulations, Title 21, Parts 210 & 211, under part 211.25 requires "each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions." The generalized nature of these requirements results in a dizzying array of training seminars, webinars, meetings, and certifications which each seek to provide guidance on interpretation of these regulations, there exists no organized approach or requirement for ensuring consistency from company to company or even site to site.

Without a solid educational foundation, the ability to consistently interpret and apply the intent of regulations results in varying approaches to good manufacturing practices. This "fractured" approach to training and education is manifested in continued quality deficiencies noted in regulatory inspections.

Can Pharmacy Schools Lead Needed Change?

Currently, the focus of most Colleges of Pharmacy in the United States remains preparing individuals to deliver clinical information and therapeutics to patients, primarily in retail or hospital settings. However, in a recent New York Times article by Noam Scheiber, "How Pharmacy Work Stopped Being So Great," the author points out that cost pressures in the changing retail marketplace are driving a reduction in the number of pharmacist positions, resulting in an unhealthy working environment for many of those remaining.

As a graduate of a great pharmacy school program (Go UB Bulls!), I believe the curriculum of these pharmacy programs was and is an excellent foundation for creating strong pharmaceutical manufacturing industry leaders. Courses in chemistry, microbiology, pharmacology, pharmacokinetics, disease therapeutics, and pharmacy practice are an invaluable educational foundation for understanding and applying the regulatory, technical, and personnel related elements needed to develop and manufacture quality therapeutics utilizing good manufacturing practices.

These colleges have worked successfully over the decades to create robust, comprehensive curriculums which create capable professionals in the retail/clinical environment. I believe the faculty of these schools, with collaboration from regulatory compliance experts from government and industry, can create an elective curriculum to educate leaders in the many quality and regulatory facets of product development and manufacturing.

Courses on data integrity, statistics, study design, regulatory filing requirements, validation principles, key elements of good laboratory and manufacturing practices, and essentials of aseptic operations among others could form the core of this curriculum. These courses could comprise an elective track for those who wish to maintain the ability to practice as licensed pharmacists, as a post graduate certification for those looking to expand their career opportunities, or as an independent course of study leading to a unique degree.

Continuing education courses offered through these schools could ensure currency in a rapidly changing environment. Ultimately, the accreditation authorities for pharmacy education could establish standards to bring national consistency to these efforts.

However, there is a need in the near term to address the currently fractured landscape of training and education. A potential solution is the creation of a consortium including regulators, industry experts and educators to identify and codify the knowledge and behavioral objectives for training and then serve as a review and certification body to help attendees chose programs that deliver the needed knowledge and skills. To supplement external education, the identification of strong subject matter consultants to mentor key leaders within the organization can be an additional solution to strengthen internal capability.

Creating Industry Leadership for the 21st Century

The development of advanced therapies and rapidly changing technologies for producing these treatments requires leaders in both development and manufacturing to have the capability to interpret and apply proper controls at all phases of the product lifecycle to meet regulatory requirements. Effective and consistent application of good laboratory, clinical, and manufacturing regulations, which constitute the foundation for producing quality therapeutics, has been an elusive goal in our industry for the last century. Together with government and industry experts, educators in our nation's Colleges of Pharmacy can provide an approach which can ultimately address the quality leadership demands of pharmaceutical development and manufacturing in the 21st century.

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Right First Time: Unlocking the Competitive Benefits of Better Batch Release

Aladdin Mandishah
Global Life Sciences Industry Solutions Manager
SAP

The soul-searching began soon after reports emerged this fall linking the tragic deaths of 70 children in the West African nation of Gambia to cough syrups produced in India. How could incidents like this be prevented from happening again?

Finding an answer to that question could very well depend on making strides on two fronts. The first is strengthening regulatory oversight of manufacturers in certain jurisdictions, a difficult proposition given the complex political, market and stakeholder dynamics in play. The second is improving batch release processes and practices, so contaminated or substandard medical products never make it out of the production facility and onto the shelves. That could be a more straightforward undertaking, for a variety of reasons. First, of course, is the desire to avoid tragic outcomes like what occurred in Gambia. As infrequent as incidents like this are, the damage they inflict in terms of human life is immeasurable. What's more, they undermine consumer confidence and extract a huge cost on the individual companies and brands involved.

These aren't the only compelling reasons for pharmaceutical manufacturers to take steps internally to streamline and strengthen the practices and processes behind batch release. Among the others:

Meeting carbon footprint, sustainability and ESG (environmental, social and governance) goals, priorities and requirements — and in doing so, potentially gaining a competitive advantage. Pharmaceutical companies are feeling pressure on multiple fronts to behave more sustainably. Using integrated, automated and standardized batch release processes instead of the siloed, manual processes that are common today can lead to substantial reductions in carbon footprint by facilitating faster supply chains, reducing inventory levels, reinforcing right-first-time releases and reducing product recalls.

Avoiding the potentially large costs associated with recalling and disposing of a substandard or contaminated batch. According to estimates from McKinsey, a single warranty or recall process can cost a medical manufacturer up to $600 million (exclusive of recall-related costs like lawsuits).

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Reducing cycle time to bring products to market faster. Based on our internal analysis at SAP, streamlining and digitizing batch release processes can reduce overall batch review cycle time by more than 90%, enabling companies to bring more products to patients, faster, with shorter order fulfillment lead times. At one large manufacturer, for example, batch review processes that used to take a quality assurance team of five people 40 hours now take a single person just one minute using intelligent digital tools.

Reducing production and inventory carrying and scrappage costs. The big efficiency gains that come from accelerating the batch release cycle time can significantly reduce operating costs by lowering the cost of meeting quality standards. We calculate that a 5% reduction in quality costs for a company with operating expenses of $80 - $100 million can result in an average of $5 million in sustainable cost savings. What's more, shorter order fulfillment lead times also can translate into as much as 25% reductions in inventory carrying costs.

As compelling as benefits like these are, for pharmaceutical companies to capture them they have to find ways to fix the well-documented shortcomings of current batch release approaches. Here's a look at how they might go about doing so:

1. **Boosting automation and standardization.** To understand just how labor-intensive and error-prone the batch release process is, consider that today close to half — 48% — of life sciences companies use manual processes for batch release and 35% check data in multiple siloed systems during the batch release process, according to our internal research. Here's where intelligent, machine-learning- and AI-driven automation tools can overcome those obstacles, giving quality assurance teams the ability to quickly collect data from disparate sources: downtime logs, line clearance logs, equipment and room cleaning logs, calibration labels, environmental monitoring data, deviations, serialization, etc. They then can draw insight from that data, evaluate exceptions and facilitate faster, more informed decisions. With a greater reliance on automation, manufacturers can shift to a review-by-exception approach to evaluating batches.

   There's also an opportunity for manufacturers to bring much-needed standardization within and across quality teams and departments, as well as along the supply chain (including contract manufacturers and suppliers) by integrating a variety of automated checkpoints into the process to ensure adherence to a set of common practices, processes, systems and functions. This in turn reinforces thresholds, parameters, workflows, etc., that lead to faster, more compliant batch outcomes.

2. **Improving visibility internally and across the supply chain.** Perhaps the most critical missing piece for more efficient and compliant batch release is a central hub from

which quality assurance teams can view and make sense of all the data they're getting from disparate sources internally and across the supply chain. From this centralized hub, manufacturers can rapidly analyze the data to make faster, better-informed decisions not only about the release of finished products to market, but also about validating the quality of externally sourced goods and internally manufactured bulk or finished products. Through the hub, quality assurance teams can more readily detect deviations early in the process, and identify erroneous batches, then track the source of error.

3. **Quality by Design.** "Quality by design is produced, not checked" should be the mantra that guides a manufacturer's approach to batch release. The U.S. Food & Drug Administration endorsed moving from a "quality after design" approach to a risk-based approach to pharmaceutical quality 15 years ago. Automation and standardization are critical to (re)designing products and processes for quality.

4. **Strengthening carbon footprint tracking and reporting capabilities.** How does producing a batch right the first time or a substandard batch impact the company's carbon footprint? How do suppliers and sub-suppliers compare in terms of their carbon footprint? What steps could your company take to minimize the resources — energy, paper and packaging, transportation, etc. — associated with each and every product? With so much emphasis being placed on sustainability, ESG and carbon-reduction, it's vital that pharmaceutical companies arm themselves with tools to answer these kinds of questions. They must be able to collect and track the make-up, and prove the origin, of the materials and equipment they use, as well as the energy their operations consume and the emissions they produce, and they also need to embed KPIs related to these factors across the business, so they can make decisions accordingly.

Incidents like the tragedy in West Africa provide a powerful reminder of just how much is at stake for pharmaceutical companies to improve their batch release processes. Now, with the advent of new approaches that promise big gains in efficiency and significant reductions in cost, they have the means and the incentive to do so.

About the Author

Aladdin Mandishah *has 15-years experience in the life sciences industry in continuous improvement roles in operational excellence and business transformation to help companies become more resilient, productive and effective. At SAP he works as a trusted advisor to customers worldwide. He shares industry best practices which companies can use to transform into Intelligent Enterprises. Ultimately, it allows them to provide better experiences for their customers and be more resilient to evolving industry trends and market conditions.*

A Practical Analytical Risk Survey Program for Active Pharmaceutical Ingredient Synthesis that Enhances Analytical Control Strategies for Early and Mid-Stage Development

Li Li, Peter Tattersall, Qinggang Wang, Jonathan Shackman, Lianjia Ma and Adrian Doggett

Chemical Process Development
Bristol Myers Squibb

Overview

Active pharmaceutical ingredient (API) process development requires a comprehensive analytical control and a set of wide-ranged analytical methods. In the early to mid-stages of development, i.e., at phase I and II clinical trials, the analytical controls in manufacturing processes are still evolving. The analytical methods designed to gather data on APIs, intermediates, starting materials, and reagents are also progressing, but knowledge regarding method robustness is limited. Despite being in clinical development, there is a requirement for scientifically sound data to provide confidence in key decisions, establish reproducible testing at contract manufacturing organizations (CMOs), and, most importantly, guaranteeing consistent quality to ensure patient safety. As every project is different, how do we drive consistency between projects in handling and learning from risk mitigation? To address this, an analytical risk survey program to evaluate common risk factors was developed. In this article, we introduce a new workflow that is simple and widely applicable to assess analytical gaps and risks for early- to mid-stage projects. The workflow combines a checklist with common risk factors and a spreadsheet with scored ranking to facilitate the collation of an experimental 'to do' list for evolution of analytical method conditions and optimization of controls. The impact of this risk survey program has shown to be value added for both the analytical teams and overall portfolio development at Bristol Myers Squibb.

Introduction

In the pharmaceutical industry, a scalable synthesis involves development of practical, safe, sustainable, and cost-effective chemistry and process design. The synthetic route, process, and analytical chemistry all evolve with the clinical development. At early clinical stages, i.e., phase I and II clinical trials, the process for small molecule APIs is usually grounded in the drug discovery route and fit for mid-scale (gram to 10's of kilogram) production needs. At the late clinical stage, the chemical process should be well defined, robust for commercial regulatory filings, and ready for full commercial manufacturing scale. The analytical controls and methods of each stage follow these needs similarly. Analytical risk assessment should have the flexibility to meet the evolving demands of process development. To account for the analytical risk assessment needs, we designed a top-down approach which we call an "analytical risk survey". This survey program is designed for early-stage projects, and the terminology of risk survey is utilized to differentiate a more involved risk assessment program for late-stage projects. In Figure 1 both process and analytical activities at different stages are summarized. Our analytical risk assessment program holistically views the analytical activities and how they collectively connect to the process to drive simple and effective method development. When viewed through the intent of the current analytical control strategy (not from an individual method), the risk survey helps highlight areas of concerns.

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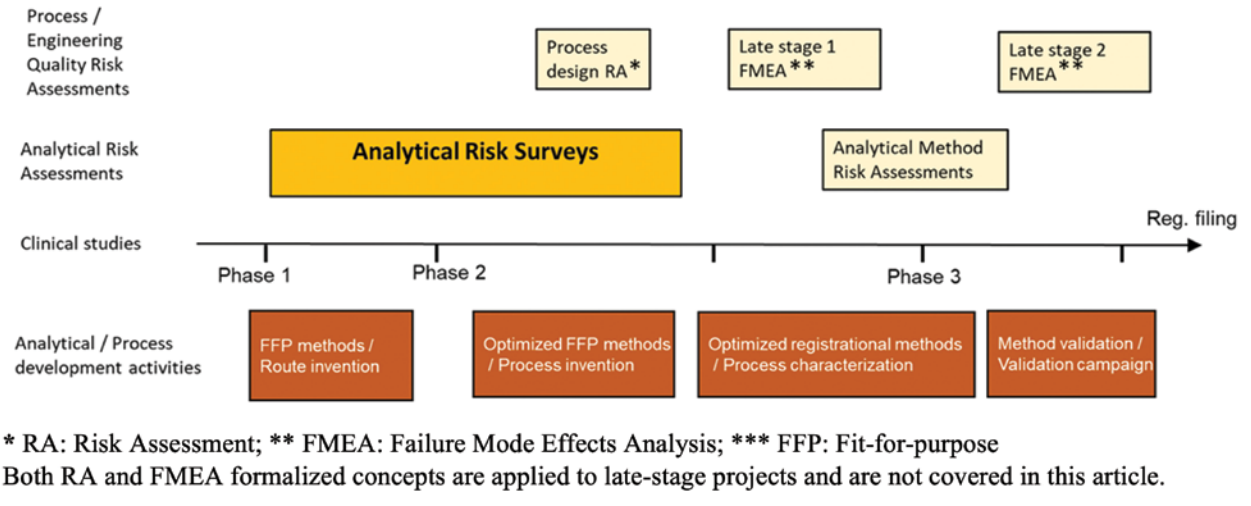

Figure 1. Process and analytical development activities and risk assessments.

In general, the risk appraisal process contains hazard identification, risk analysis, and risk evaluation components. These concepts have been applied to many areas of business, government, and industry to identify any significant hazards to working projects.[1] Our early development analytical risk survey process also utilizes these concepts. Risk and hazard identification is achieved by evaluating categories that include methods, knowledge gaps, control test placement, control test criteria, and impurity assessment as required by ICH guidelines Q3A, Q3C, Q3D and M7.[2-5] The analysis methods that are used for characterizing organic impurities, inorganic impurities, residual solvents, and mutagenic impurities are evaluated with respect to being scientifically sound and suitable for their intended purpose. Some of these may be considered as critical quality attributes (CQAs). Organic impurity tests, including starting materials, by-products, intermediates, degradants, reagents, ligands, catalysts, enantiomers and mutagenic impurities are all considered to be and included in the common risk categories. Inorganic impurity tests, residual solvent analyses, in-process controls (IPCs), and manufacturing equipment cleaning methods may also be considered.

Once identified, risk analysis is the second important component in the risk appraisal process. Risk analysis is the assessment of the risks associated with possible hazards. It is the qualitative or quantitative process of evaluating the likelihood of occurrence and severity of harms.[1] In our risk survey program, the method performance parameters and validation requirements in ICH Q2(R1)[6] are used to evaluate the risk severity within each of the risk categories. A baseline performance of the analytical methods is reviewed to evaluate the severity of the risks. At early clinical stages, the control strategies are preferred to be objective and simple to execute, yet also aligned with ICH guidelines. Most analytical methods are fit-for-purpose (FFP) at this stage, due to the evolving process chemistry. Therefore, our risk severity evaluation must consider these factors and make the risk analysis phase-appropriate.

The third component of risk assessment is risk evaluation. Here the evaluation attempts to define the estimated risk to analytical method performance. Assessment of the analytical methods can enable the introduction of controls that mitigate risk. Our risk evaluation is a combination of actual method performance and the stage-appropriate scientific and quality expectations. In our risk survey program, we compare the identified and analyzed risk characteristics against risk criteria previously collated based on cumulative experiences with historical projects. A subject matter expert (SME) committee reviews the risk estimation presented by the project team and together they adjust as needed. With the aligned risk, which is simply marked as low, medium, or high, the project team will work with SMEs to determine the actions required for risk mitigation.

Discussion

Risk acceptance of early-stage analytical methods

It is commonly understood that risk is defined as the combination of the probability of occurrence and the severity of a harm.[1] Probability of analytical risk correlates strongly with the complexity of analytical methodologies (e.g., a gas chromatography method is more complicated than loss on drying) and also with an analyst's performance or experience (i.e., more experience can generally reduce analytical risk.). Criteria for evaluating risk probability are defined in Table 1 rows with tan shading. Severity more closely correlates to the purpose of analytical tests (e.g., release control tests have higher risk than knowledge gathering tests), placement

in a synthetic route (e.g., closer to a final API step is riskier than earlier steps), and stage of development or clinical trial (severity of risk is higher at later stages). Gauges to assess risk severity levels are defined in Table 1 rows with blue shading. These considerations or differentiators can be used as a tool for analytical teams to help assess their analytical risks (see Table 1).

Table 1

Risk Differentiator		Lower Risks	Medium Risks	Higher Risks
Probability	Method type/ complexity/ instrument	General and familiar methods using common instruments	Common and/ or simple methods using widely available instruments	Specific and/or complex methods requiring unique instruments
	Performance/ experience	Well understood	Reasonably well understood	Not common or well understood
Severity	Stage	Early-stage development	Mid-stage development	Late-stage development
	Proximity to API	Early-steps	1-2 steps from API (Quality control steps)	API step
	Needs / purpose	Gather knowledge only	Control method	CQA test

Figure 2 helps to visualize the "line of acceptable risk" generated using complexity of analytical methodology and performance risk with project stage.[7] This highlights that risk tolerance at early stages is relatively larger and decreases as clinical development progresses, which Table 1 captures for risk survey assessors. The risk survey program is designed to meet the early stage needs by performing a "top down", holistic analytical control evaluation. Late-stage projects, however, have much lower tolerance to analytical risks and must be suitable for routine quality control analysis, which is beyond the scope of this article.

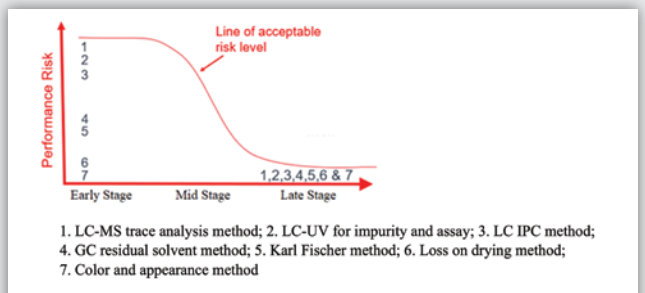

Figure 2. Acceptable analytical method performance risk across stages.

Risk categories of early and mid-stage projects

Risk categories are utilized to aid in risk identification. The risk categories were collated from: molecular structure and related unique material properties; historical data, as would come from method transfer experience; ICH guideline requirements, including release specification guidance; and other drug substance analytical activities. Covered within these categories are:

- Method types, which can range from stability-indicating methods to specific trace impurity analysis (e.g., nitrosamines).
- Method analytical target profiles, which are typically linked to process control limits or release specifications.
- Physicochemical properties that can include presence of UV chromophores, solubility, hygroscopicity, static nature, etc.

Table 2 lists the most common analytical risk categories we have encountered to help project teams evaluate soft spots in their controls and acts as a common check list to drive consistent practices across teams. Note, some of these categories may overlap, such as enantiomeric control and chromatographic selectivity.

Risk banding

Risk analysis is the qualitative or quantitative process of measuring the likelihood of occurrence and severity of harms and must be performed across each of the identified risk categories. The evaluation of the harm and potential impact to quality should be based on scientific knowledge and ultimately link to the protection of the patient.[1] In our analytical group, the risk level of each category is measured by comparing the analytical method's observed performance to expected quality and scientific requirements, as well as historical experience. For example, widely spaced analytes in an isocratic LC method are much lower risk than a multiple stage gradient LC method just meeting baseline resolution requirements.

When the observed performance of the method is significantly better than the regulatory and scientific requirements, the risk level is banded as "low". When the performance of the analytical method meets but approaches the limit of regulatory or scientific expectancy, the risk level is defined as "medium". When the performance of analytical method fails to meet either regulatory or scientific expectancies, the risk level is defined as "high". High risk scenarios can occur with rapidly changing projects and expectations. For example, process changes can generate entirely new impurity profiles, which may challenge existing methods. Even a defined process can become high risk if robustness studies performed near to the risk survey identify gaps (e.g, co-eluting impurities are found during a peak homogeneity check). Additionally, acceptable risk in the earliest phase may present as high risk if they are nearing a transfer or stage transition due to tightening requirements. Table 3 lists a few illustrative examples of risk banding. Over time, we have compiled the more common risk categories and criteria across method type combinations (e.g., LC-UV for organic impurities or GC-FID for residual solvents) to aid analytical teams' assessments. The selected parameters are generally the more technically challenging aspects of the method or the more important quality aspects of the method. For less common category and method combinations, historical data is evaluated, literature is surveyed, and/or additional SMEs are consulted.

Implementation of risk surveys

The analytical risk survey was founded on both a scientific and practical approach for evaluating present and future process control

Table 2. General risk categories for small molecule analytics

Analytical Categories		Typical Example Techniques	Higher Risk Examples
Specification Related	Enantiomeric Control	LC / GC	Poor resolution and / or sensitivity for enantiomeric pairs
	Organic Impurities	LC / GC	Wide range of UV response factors affecting linearity and / or sensitivity
	Mutagenic Impurities (MI)	LC / GC	Sensitivity is not adequate for the specification and / or complicated sample preparation or detection methods
	IPCs	LC / GC	Matrix incompatibility with common chromatography diluents and / or analyte stability
	Equipment Cleaning	LC / TOC	Poor solubility in reverse phase LC friendly solvents and / or low specifications (e.g., MI swab testing)
	Residual Solvents	GC / LC	Class 1 solvents meeting 10% of ICH Q3C levels
	Counter Ion	LC / IC / Titration	Less common detection (e.g., LC-CAD or specialized electrode)
	Key Raw Materials	LC / GC	Thermally labile analytes with poor UV response
	Elemental Impurities	ICP-MS / OES	Challenging matrices (e.g., high salt formulations)
	Form	XRD	Difficult to process samples (e.g., extremely hard)
	Particle Size	LLS	Uncommon presentations, such as nanoparticles or dispersions
	Bioburden and Endotoxin	Bioassay	High water content in last two steps of synthesis
Physicochemical Related	Poor Chromophores	LC / GC	Less common and / or non-linear detection
	Challenging Chromatographic Selectivity	LC / GC	Regioisomers, diastereomers, and other closely related structures
	LogP / LogD / pKa	LC / GC	Inability to retain at mobile phase pH and / or inability to dissolve in compatible diluents
	Powder Properties / Hygroscopicity / Viscosity	LC / GC	Materials difficult to accurately weigh and / or pipette
Method Transfer Related	Method Robustness Concerns	Any	Poor method repeatability, stability, and / or narrow operating tolerances
	Instrument Availability	LC / GC / CE / SFC / NMR	Less common (GxP) instruments (e.g., SFC) and / or detection (e.g., LC-ELSD or GC-NPD)
	Consumable Availability	Any	Specialized and / or localized materials (e.g., small column vendors or single supplier derivatization reagents) and / or availability of standards
	Unit Operations	Any	Highly convoluted sample preparations with strict time limitations

Table 3. Examples of risk banding across analytical categories.

Risk Category		Method Performance Risk Band		
		Low	Medium	High
Specification Related	Enantiomeric Control	Isocratic method; target analyte(s) R_s > 2.5; LOQ < 0.1%; RSD of retention time and response factor <<2.0%	RP gradient method; resolution between 1.5 < R_s < 2.5; LOQ < 0.15% or < specification; RSD of retention time and response factor < 2.0%	NP gradient method; R_s < 1.5; LOQ > than 0.5% or anticipated specification; RSD of retention time and response factor > 2.0%
	Mutagenic Impurities (MI)	Target analyte(s) R_s > 1.5; LOQ < 30% of specification; recovery > 80% and < 120%; RSD of retention time and response factor <<2.0%	R_s > 1.5, LOQ = specification; recovery > 70% and < 130%; RSD of retention time and response factor < 2.0%	R_s < 1.5; LOQ is higher than anticipated specification; recovery < 70% or > 130%; RSD of retention time and response factor > 2.0%
	IPCs	Target analyte(s) R_s > 1.5; LOQ << call point; target analyte(s) retention times and response RSD << 2.0 %	Target analyte(s) R_s > 1.2; LOQ < call point; target analyte(s) retention times and response RSD < 2.0%	Target analyte(s) R_s > 1.0; LOQ = call point; target analyte(s) retention times and response RSD > 2.0%
Physicochemical Related	Poor Chromophores (Organic Impurities)	LOQ << specification; LC-UV > 220 nm	LOQ < specification; LC-UV > 210 and < 220 nm	LOQ = specification; LC-UV < 205 nm or non-UV detection
	Challenging Chromatographic Selectivity (Organic Impurities)	Target analyte(s) R_s > 1.5 with any peak in main peak tail > 2.0; peak purity check passes; RSD of retention time and response factor <<2.0%	Target analyte(s) R_s > 1.2 with any peak in main peak tail > 1.5; LC-UV peak purity check passes; RSD of retention time and response factor < 2.0%	Any target analyte R_s < 1.2; LC-UV peak purity check not performed; RSD of retention time and response factor > 2.0%
Method Transfer Related	Method Robustness Concerns	Phase appropriate validation completed and all parameters met acceptance criteria; successful transfer to at least one vendor or other internal teams and / or tested on multiple brands of instruments	Qualification completed and all parameters met specifications; limited transfer activity and / or limited alternate instrumentation tested	Qualification completed and some parameters only partially met specifications; no transfer activities or alternate instruments tested

Limit of quantification (LOQ). Relative standard deviation (RSD). Resolution (R_s).

plans and methods. In order to maximize its adoption, the survey workflow was designed to be simple, effective, and easily performed (Figure 3). At a high level it is performed as a two-part process. In the first part, the project team prepares the discussion materials while in the second part, the project team presents to a team of analytical SMEs and discusses the risk survey of the project to generate alignment and possible follow-up activities. The overall workflow includes the following major activities prior to the risk survey committee meeting:

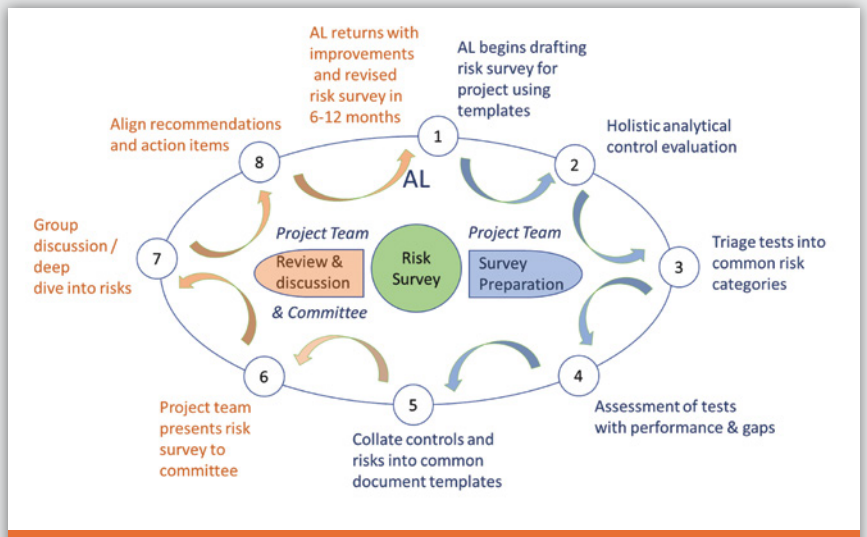

Figure 3. The analytical risk survey workflow.

- **Holistic analytical controls evaluation:** Each project team's analytical lead (AL) initially evaluates the holistic analytical controls within the context of the API release requirements and CQAs with respect to ICH guideline Q6 and phase of development. All the tests in the analytical controls, including intermediate release and IPCs, are chosen to impart the quality, safety, and efficacy of the drug substance. Relevant data should have been already collected as part of the development and campaign knowledge.
- **Triage tests into common risk categories:** All testing methods are evaluated and placed into the relevant project risk categories shown in Table 2. The performance history of each method is assessed, and key analytical concerns captured for a project using a templated format. Table 2 provides a list of key analytical categories that are common areas of concern; however, as every project is different, the category population can differ.
- **Assessment of tests with performance and gaps:** For each individual method, the performance is compared to that expected (see examples in Table 3). Any unusual method conditions, such as uncommon instrumentation, hard to source materials, atypical operating parameters, or parameters near the edge of typical calibrations are specifically evaluated. Where possible, data from the method innovator lab and from other vendor labs is compared to check the method reproducibility. With the above information and the risk band catalog, the risk factor level of each method is standardized to drive consistent evaluation and expectations.
- **Collate controls and risks into common document templates:** Knowledge gathered from the activities above is used to generate a slide deck from a pre-generated template that includes project background information and risk factors. Banding for each risk characteristic is additionally collated into a spreadsheet template where detailed reasoning of the risk band is explained.

On average, ALs will only need a few hours to collate the requisite information and make or update their template-based documentation (for return visits). Once the AL and their project team have gathered all their required information, the risk survey committee meeting is held. During the meeting, ALs present the assembled risk evaluation using the common document templates to a team of experienced SMEs who have a strong background in analytical method development, validation, and transfer activities. SMEs evaluate the control strategies and the risk banding of each method during the meeting so they may provide their opinions on the project team's evaluation. SMEs also provide feedback and suggestions to ALs on the control strategies, gaps, method risk banding, and risk mitigation. For all cases where high risks exist, a mitigation plan is required.

The ultimate goal is to ensure alignment between the project team and expert committee on the recommendations and action items, with a commitment for the AL to return with improvements and a revised risk survey in 6 to 12 months if the project is still active. The risk survey meetings are typically 1 to 1.5 hours with approximately 30 minutes presentation time and 30 minutes discussion. The ALs will record all the action items in the spreadsheet comments section. The spreadsheets and presentation decks are stored on a commonly accesible platform, such as a Microsoft SharePoint site.

Risk survey program metrics

So far this program has provided help to more than 40 projects within BMS over 5 years. The collated results of medium to high-risk areas across the portfolio of projects has enabled periodic evaluation by the department leadership. This has helped justify improvements in trainings, SME resourcing, technology and method development workflows across the department and projects.

In Figures 4 and 5, the method performance risk bands identified throughout the year and across many methods are plotted against the risk categories for 2020 and 2021, respectively.

In 2020 the area with the most prevalent high risk was due to analyte degradation either in solution or on the LC column. This degradation may be caused by: intrinsic compound instability; incompatible mobile phases, diluents, or other sample preparation operations; or due to a specific reactive property of the column, such as residual metals. When dealing with such risks, root cause analysis experiments are

suggested based upon the data at hand. For example, alternative chromatographic conditions or inert systems can isolate the separation from the sample preparation.

Communication of common liabilities also leads to more awareness of common risks, which allows us to identify opportunities to implement method development strategies to reduce the probability of risk. For example, a workflow change was implemented to reduce the second highest risk contributor in 2020, method selectivity, which was primarily identified in achiral LC methods. An improved LC column screening system was introduced over these two years,

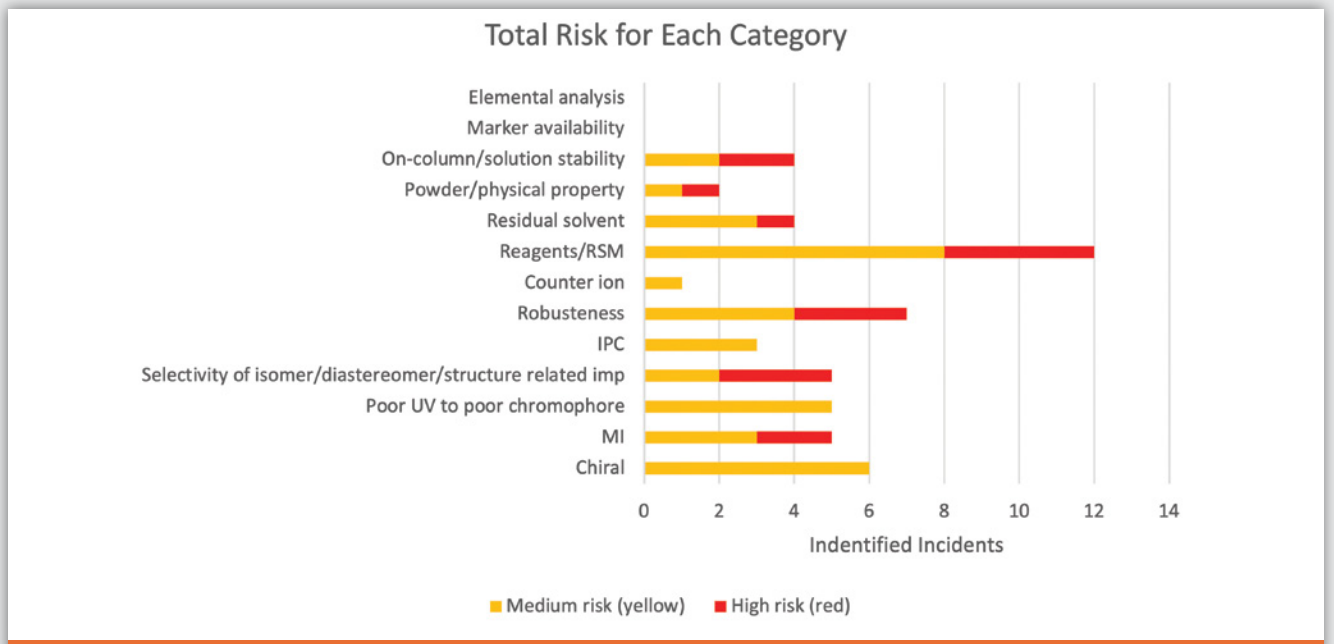

Figure 4. Year 2020 Metrics from Risk Surveys – Totaled from Medium and High Risk

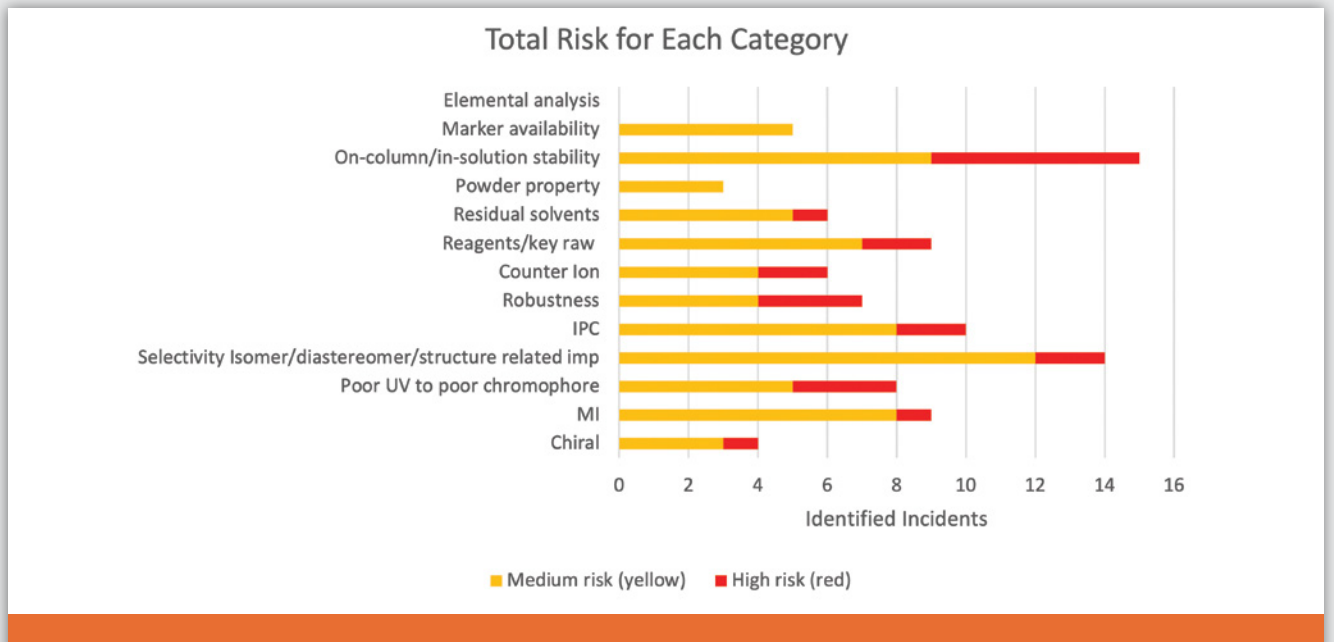

Figure 5. Year 2021 Metrics from Risk Surveys – Totaled from Medium and High Risk

as well as a 2DLC main peak purity check to ensure appropriate method selectivity at the earliest stages of development. To address IPC control risks, a training program was implemented to ensure method developers were better equipped to deal with the unique characteristics of IPC methods. These examples highlight how the risk survey program has led to and captured improvements in our performance. However, this analysis also reveals that high and medium level concerns were not completely eliminated and will require more attention moving forward.

Conclusions

Here we have presented a risk survey program applied to the analytical strategy for early to mid- stage development programs. It is a simple assessment on the performance of analytical methods to meet their desired stage-appropriate objectives, and it also serves to capture knowledge and understanding of the method's merits to improve future development. The risk survey can deliver clear and actionable outputs because it's driven by evaluating real-world method performance against consistent scientific expectations and criteria. By performing risk surveys across a large and diverse portfolio (>40 projects to date), the program has been able to identify not only concerns within a given project, but also has the additional benefits of driving consistent and improved work practices across the analytical community.

We believe this program can be readily extended beyond small molecule drug substance programs, such as biologics or drug product analytical groups, due to similar quality requirements and analysis techniques, although some modification of categories and banding criteria would be necessary. By using the risk survey process, any analytical team can reduce analytical risk in early development, facilitate stage-appropriate analytical controls, drive inter-project consistency, and identify improvements to method development workflows.

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A CDMO Perspective on Developing Biological Modalities from Discovery to Commercialization

Jim Huang, PhD and Shaukat Ali, PhD
Ascendia Pharma

Introduction

Biological modalities with poor solubility and bioavailability are presenting challenges to drug manufacturers to move them from discovery to manufacturing. Drug sponsors are looking to contract manufacturers to help them overcome this problem as many offer tailored and customized approaches to expedite the launch and commercialization of these drug molecules.[1] As the cost of developing new chemical entities (NCEs) keeps rising, reaching over $2B for a single molecule and taking over 10 years with fear of a patent cliff, drug manufacturers are also weighing options for outsourcing the formulation development to get better return on investment (ROI).[2] Together with the rising cost and risks on development, drug manufacturers are exploring all avenues to reduce time and cost to expedite the commercialization and marketing of drug molecules, while focusing on prioritizing projects and investment on their most innovative and blockbuster products. This trend is contributing to a seismic shift in the industry that is fueling potential growth in the contract drug manufacturing organization (CDMO) industry.[3]

Weighing Options for a CDMO

As costs continues to rise in development of new molecules, finding a CDMO partner that "fits for all" with the expectation of saving time and resources, and meeting project deadlines, continues to be challenging. For instance, molecules with poor solubility and bioavailability, weighing options on employing an appropriate formulation technology and finding a right partner with technical know-how and expertise, remain an impediment. For example, developing a drug in liquid or solid oral, and/or in parenteral form, requires a careful design of experiments (DOEs) for an optimal formulation to meet the critical quality attributes and the clinical end points to satisfy the FDA's guidelines. This creates the opportunities for CDMOs with enabling technical capabilities in developing multiple dosage forms for different modalities with their proprietary formulation and development capabilities. In those cases, early phase development, as a feasibility to proof of concept (POC) followed by evaluation for scale-up, bear risks but is highly plausible and rewarding with a CDMO partner offering the right expertise in formulation development, analytical services and processing capabilities. With continued interest in the development of biologics, identifying one CDMO from early stage to scale-up and manufacturing could also require full assessment of their internal technical, analytical and cGMP manufacturing capabilities.

CDMO's Capabilities and Relationship with Clients

Technological challenges stemming from physico-chemical properties of new molecules coupled with limited resources within the contract manufacturers, and/or a reliable supply chain, can lead to additional delays in development and manufacturing of clinical supplies, initiation of clinical trials, and hence, the approval and marketing of new drug candidates. Thus, adapting the strategies with a first tier and second tier approach to CDMOs based on their capabilities and expertise, should be a prime consideration for building trust and partnership while aiming to mitigate the timeline and meet the developmental processing and cost.[4] For example, building trust and a better relationship based on their offerings will lead to further business potential and expedite the drugs faster to market, and hence, ultimately lead to multiple business opportunities in the future. With both the R&D expertise, and cGMP manufacturing capabilities suited

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for a particular dosage form, those CDMOs will help guide the drug manufacturer to make the right decision. It is equally important to continue building the relationship in earnest with CDMOs to define tasks and deliverables to achieve the long-term goals, in general.

Sterilization and Aseptic Processing

Sterilization is a key step in the manufacturing process to ensure that pharmaceuticals and biopharmaceuticals are safe to use.[5] The key parameters considered during sterilization are temperature, time, and pressure to minimize the bioburden assay. Other parameters are holding time between vial/bag filling and sterilization. The hold time depends upon the media used; for instance, saline for injection could be held longer than dextrose in water due to the possibility of microbial growth and increasing bioburden. Terminal sterilization of drug products is often carried out at 121℃ for 15 minutes but if the API is sensitive to higher temperature, the moist heat sterilization can be conducted at lower temperature (ca. 115℃) for a longer duration or opted for sterile filtration, if required.

Aseptic processing is a process that involves careful and well controlled engineering for the equipment used, facility, and assemblies including the filling stations and chambers, and closures of the vials or bottles to prevent any unwanted consequences of batch failures and compromise quality risks. In most cases, human borne contaminants are most critical and require immediate control to mitigate the risk factor in aseptic processing.[6]

Regulatory guidelines are recommended for drugs in closed aseptic container systems to reduce the risk for cross-contamination with microbes that could lead to possible batch failures. The manual sampling is also a cause for cross contamination, and therefore, the FDA is advocating for closed single-use sampling systems.[7] European agency recommends that the bioburden should be monitored before sterilization and the working limit on the efficiency should be defined before the sterilization.[8] In addition, the sterilization of drug products in premixed bags requires further scrutiny by the agency to confirm that no leachables or extractables are generated during terminal sterilization.

There are two ways for achieving sterilization, one in which the products filled in the containers are sterilized and second, the drug product is preferably sterilized before filling under aseptic processing conditions to avoid any cross contamination. Cundell reviewed the justification for use of aseptic filling for sterile injectable products and compared with terminal sterilization using moist heat conditions.[9] A better and more efficient sterilization can be achieved by terminal sterilization only if the compatibility, physicochemical stability and packaging and storage of products and suitability of delivery systems are met for APIs and excipients. Unlike terminal sterilization, aseptic sterilization can be widely applicable to all products highly sensitive to higher temperatures, as a result the API's degradation can be minimized, and stability can be maintained.[10] It is widely practiced within the guidelines set forth in the FDA's aseptic processing manual.[11]

General Considerations for Selecting a Partner for Sterile Products

Key considerations in identifying the right CDMO partner require a level of mutual understanding about the scope of work (SOW). CDMOs with innovative technologies, for instance, have generated the opportunities with the clients interested in aseptic manufacturing of sterile products, providing assurances in formulation development and overcoming the challenges to deliver high quality medicines for temperature sensitive APIs. In cases where APIs are thermally stable in containers and packaging, sterilization by steam or moist heat or irradiation is an option for preventing contaminants from microbial growth or microbes. On the other hand, APIs sensitive to higher sterilization temperature, the aseptic filling is ideally used to maintain the sterility of all components. Lyophilization of certain molecules could further improve the stability of drug products that aid in storage, shipment, and shelf life of drug products. Thus, a CDMO with enabling capabilities in lyophilization and sterile fills through aseptic processes, can offer services to clients working on small and large molecules and biologics as well. A one-stop-shop CDMO, having the integrated lyophilization and aseptic manufacturing capabilities under cGMP that meets the ISO 5, ISO 7 and ISO 8 classifications as shown in Table 1, can further expedite the development and marketing of drugs faster.

Ascendia's Capabilities in Formulation Development and Manufacturing of cGMP batches

As sterile manufacturing demand continues to rise and remain strong, CDMOs continue to expand their capacities by investing in high-speed, latest isolator manufacturing technology with fully automated packaging lines. Ascendia, like other CDMOs, has been expanding its footprint in sterile manufacturing capabilities by providing services to emerging and specialty and biopharma companies requiring cGMP manufacturing from pre-clinical tox studies to first-in-humans (FIH) and late-stage clinical batches as shown in Table 2.

With proprietary platform technologies in long-acting injectables, lipid nanoparticles, or nanoemulsions for complex therapeutic modalities, Ascendia's capabilities are at the par.[13] Ascendia's cGMP manufacturing capabilities, for example, include oral liquids, capsules and tablets, and sterile injectable dosage forms for Phase 1 and Phase 2 and Phase 3 clinical supplies with commercial launch readiness by Year 2023. Ascendia's capabilities and commitments to B.E.S.T. customer service principles (brilliant technology, excellent service, superior quality and trust), therefore, can bring the innovative molecules to human trials faster, leading to expeditious commercialization of drugs for its clients.

Ascendia's most advanced aseptic fill stations include ISO qualified clean rooms and isolators, to fill up over 9000 vials per hour with

Table 1. ISO classifications of clean rooms[12]

Air cleanliness	Maximum # of airborne particles (/m³)			
	Count under non-operating conditions		Count under operating conditions	
	> 0.5 microns	> 5 microns	> 0.5 microns	> 0.5 micron
ISO 5 (Grade A)	3520	20	3520	20
ISO 7 (Grade B)	3520	29	352000	2900
ISO 8 (Grade C)	352000	29000	3520000	29000

Table 2. Ascendia's sterile and non-sterile processing and fill & finish capabilities

	Pilot sterile	S1-Sterile	S2-large Sterile		Non-Sterile Early Phase I/II	Non-sterile2-commercial
# of suites	5 suite (with freeze dryer) (PFS/Vial)	4 suite (PFS/Vial)	5 suite (Vial)	**# of suites**	5 suites	8 suites
Classification	100/10,000	100/10,000	100/10,000	**Classification**	100,000	100,000
Capabilities/output	Up to 5,000 units per batch	up to 24,000 units per batch	Up to 150,000 units per batch	**Capabilities/output**	Pilot batch size, up to 100,000 units per batch	>=100,000 units/batch
Size main processing area	1,000 sq. ft.	1,500 sq. ft.	10,000 sq. ft.	**Size main processing area**	4,000 sq. ft.	15,000 sq. ft.

complete automation. In addition, the lyophilization unit provides the extended capacity of over 5000 vials for each freeze drying cycle.

Conclusion

Ascendia continues to play an important role as a specialty CDMO in formulation development and cGMP manufacturing of complex dosage forms such as lipid nanoparticles, liposomes, nanosuspensions, nanoemulsions, and long acting injectables based on its proprietary technologies: Emulsol®, Amorsol® and Nanosol®, leading to translation of novel therapy modalities from discovery to clinical phases and commercialization at a faster speed. Its state-of-the-art facility, processing equipment and technical know-how in lyophilization, aseptic processing, and sterilization under cGMP demonstrates its full commitment to clients seeking support in human clinical trial supplies and commercialization for oral and parenteral dosage forms.

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Author's Biographies

Jim Huang *is the founder and CEO of Ascendia Pharmaceuticals, Inc. Dr. Huang received his Ph.D. in Pharmaceutics from the University of the Sciences in Philadelphia (formerly Philadelphia College of Pharmacy and Sciences) under Joseph B. Schwartz. He has more than 20 years of pharmaceutical experience in preclinical and clinical formulation development, manufacturing, and commercialization of oral and parenteral dosage forms. Dr. Huang's research interests are centered on solubility/bioavailability improvement and controlled delivery of poorly water-soluble drugs through nano-based technologies.*

Shaukat Ali *joins Ascendia Pharmaceuticals Inc. as senior director of scientific affairs and technical marketing after having worked in the pharma industry for nearly 30 years. His areas of expertise include lipid chemistry, liposomes, surfactants base drug delivery systems, SEDDS/SMEDDS, oral and parenteral, topical and transdermal drug delivery, immediate and controlled release formulations. He received his PhD in Chemistry from the City University of New York and carried out his postdoc training at the University of Minnesota and Cornell University. Dr. Ali has published over 45 articles in the scientific journals and is inventor/co-inventor of several US and European patents. He is the recipient of IPEC's Henk de Jong industrial research award and serving as a member of the USP panel of expert for Excipient Test Methods committee.*

Raman Spectroscopy Streamlines Process Monitoring in Biopharmaceutical Manufacturing

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Raman spectroscopy is widely used in many applications – including biopharmaceutical manufacturing – that require analysis of the chemical composition of solid, liquid or gaseous materials. This non-destructive analytical technique can not only provide detailed information about the chemical structure, but also give insight into the phase and polymorphy, as well as crystallinity and molecular interactions. The drawback is that it often involves complex analytical workflows and requires the use of highly specialized equipment together with expert knowledge in Raman spectroscopy techniques. New technologies have been introduced to the market in recent years, making Raman technology more accessible to a wider public through analyzers with intuitive control and user-friendly interfaces. This article talks about the need for modern process analytical technologies that are accurate and reliable – while being more accessible to lab technicians – and how they can be used for biopharmaceutical process monitoring.

Biopharmaceutical manufacturing has revolutionized modern medicine through novel active ingredients that have enabled highly specific and effective treatments for a range of diseases, including cancer and autoimmune disorders. Biopharmaceuticals are created by host cells that are made to express the desired product, which is subsequently isolated, purified, and then formulated to ensure a consistently safe and efficacious medicine. When working with living organisms, the environment must be just right as even small variations in parameters such as pH, temperature, dissolved oxygen, feed composition and feed timing can affect the yield and quality. It is therefore crucial to understand every aspect of each step in the process to ensure optimal process control and avoid costly mistakes, including failed batches, inefficient use of resources and end products that do not pass quality control checks.

Careful Process Monitoring

Process production is a method used for bulk manufacturing of goods such as pharmaceuticals, foods and beverages, refined oil,

gasoline, chemicals, and plastics. It makes use of a specific formula or recipe to create a product from a combination of ingredients or raw materials, involving numerous checks throughout the entire process, starting by establishing the quality of the raw materials and intermediate compounds, all the way through to testing the purity of the end product. The process analytical technologies (PATs) used for this purpose must be accurate and reliable, as well as adaptable, as they will be employed at different manufacturing stages. An example of a technology that is flexible enough to be used for process production is Raman spectroscopy.

Raman spectroscopy is a powerful analytical tool that provides rapid and precise analysis without being destructive to the sample. It has significant advantages over other spectroscopic methods, such as infrared (IR) and near-infrared (NIR) spectroscopy, as it offers specificity, compatibility with aqueous systems, and sampling flexibility, making it the method of choice for process monitoring.

Identifying Molecules

Raman spectroscopy helps extract information about the chemical structure, phase and polymorphy, crystallinity and molecular interactions by observing how laser light interacts with the matter. The laser beam is delivered to the sample using a fiber-optic cable with a probe at its end, and the incoming energy causes the molecules to vibrate and scatter the light, which is collected and interpreted by a detector. The scattering can be either elastic, with the energy of the molecule unchanged after interaction with the photon, or inelastic, where the molecule absorbs some of the energy and the scattered photon loses energy, resulting in a color change. The latter process is important as it provides valuable insight regarding the molecules present, generating a so-called Raman spectrum – a collection of peaks at certain photon frequencies that is unique to each molecule and can be used as a fingerprint to identify it. In this manner, it is not only possible to identify which molecules are present, but also in which amounts.

Small Footprint, Large Impact

Raman technology is non-destructive, which makes it ideal for continuous process monitoring with in-line or on-line analysis. It can be integrated directly into a production line and delivers results in a manner of seconds. The downside is that, up until now, this technique has demanded complex, bulky and expensive equipment, as well as a specialist technician to operate and maintain the instrument. These requirements compromised the reliability of this approach and increased the operational costs. The introduction of compact, easy-to-use, reliable and affordable systems changed the Raman technology landscape, making it accessible to a wider public. These new devices are not only smaller but also designed with less experienced operators in mind, offering

an intuitive user interface that allows non-experts to benefit from everything that Raman technology has to offer. Manufacturers can now easily integrate this technology into their production process, increasing efficiency and product quality.

Detailed Process Information

Raman spectroscopy can handle samples in different forms, including solid, liquid, gas, powder, aqueous solutions or slurry, and each peak in the spectrum provides detailed information about the substances that are present. This flexibility allows testing at various points in the production process to monitor the analyte of interest, which is especially beneficial when dealing with a bioreactor that often contains many types of molecules. Quantifying the amount of a certain substance from a Raman spectrum is straightforward as there is a linear relationship between the intensity of a peak and the concentration of the corresponding molecule. It is therefore easy to build quantitative models that accurately predict the concentration even when dealing with a relatively small sample set. These useful features open up a range of possibilities and can be used throughout the entire biopharma manufacturing process to verify the integrity of raw materials, monitor bioreactor processes in real-time and evaluate the end product. Raman spectroscopy can answer questions such as 'Are the cells supplied with the right amount of glucose?', 'Are too many secondary metabolites building up?', 'Have the cells begun to produce the desired product?' and 'How much product has been produced, and does it have the right characteristics?'. As all the answers are provided in real time, it is possible to make continuous adjustments to optimize the processes.

Monitoring Across the Entire Production Chain

Process analysis involves several types of measurements that can be divided into four primary classes, defined by their location and whether the sample needs to be removed from the production line for testing:[1]

In-line measurement

During in-line measurements, a probe or sampling interface is placed either inside or in line with the process or product flow. This usually means inserting a probe directly into a flow system or bioreactor, to continuously monitor the product. Using Raman spectroscopy at this stage allows evaluations at several different locations in parallel to determine product consistency throughout the process. This is possible because neither probe nor sample needs to be removed during the measurement process.

On-line measurement

On-line measurement is similar to in-line monitoring, but with some differences; although the sample can still be measured without being removed, a part of the product is redirected for analysis. This means that measurements are performed on just a portion of the product, and the diverted sample can be re-introduced to the process stream or diverted to waste, depending on the application.

At-line and off-line measurement

Contrary to in-line and on-line measurements that do not require the sample to be removed for analysis, at-line and off-line measurements involve checks away from the production line. In case of at-line measurements, the tests are run in close proximity to the production facility, while for off-line measurements the sample is transported to a remote laboratory. Compact Raman analyzers – for example miniaturized handheld Raman analyzers with quantitative analysis capabilities – are ideal for effective measurements in either of these environments.

Optimizing Glucose Levels

Raman spectroscopy has proven to be useful for many different applications in biopharmaceutical production, and one example is modeling of the glucose content of a bioprocess. Glucose is required for cell reproduction and is subsequently added through a feeding cycle to keep a constant rate of cell production. Keeping glucose at the right level is of utmost importance for most processes as it is directly connected to the yield, and modeling its content can therefore help gain precise control of the production rate.

Modeling requires data which, in this example, has been collected from a bioprocess performed at varying global locations,[2] using the same instrument set-up at each site (see Figure 1). The stability and accuracy of the analyzer ensured consistency of results between the different locations. Additionally, fundamental preprocessing methods were used to target and amplify the relevant signals within the Raman data. This means that, although the individual data sets were small, the gathered information could be combined, resulting in a precise

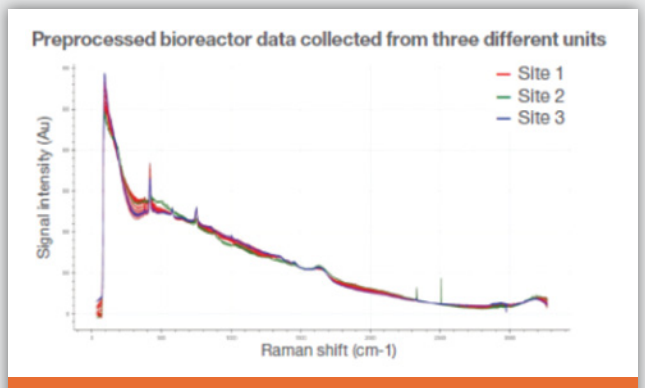

Figure 1. Preprocessed bioreactor data collected from three different units.

predictive 'global' glucose model that could be used at any location using that specific set-up.

This powerful tool can offer real-time tracking of the glucose concentration throughout the bioprocess by analyzing the output. Application of this model to a fourth site is illustrated in Figure 2, showing how the glucose level steadily declines over time until a specified minimum value is reached, rising again after the addition of glucose. Using Raman spectroscopy this way ensured optimal process control.

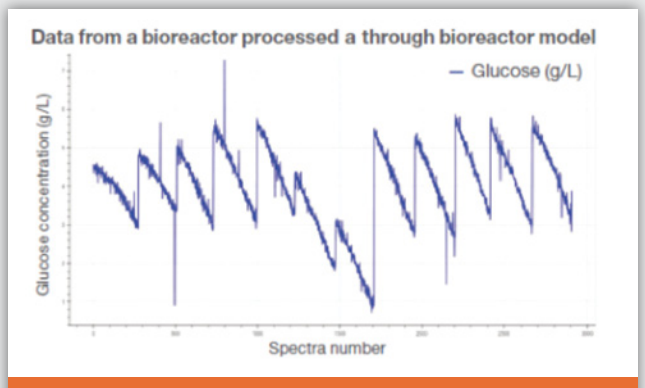

Figure 2. Application of the glucose model to bioprocessing.

Summary

Raman spectroscopy has proven to be useful in various applications in both research and manufacturing, including process control for biopharmaceuticals, where it offers enhanced, non-destructive compositional measurements for a variety of sample types. This technology has several advantages over other spectroscopic methods, such as infrared and near-infrared spectroscopy, providing specificity, compatibility with aqueous solutions, and sampling flexibility. In addition, modern analyzers based on this technology are easier to use compared to old models that required expert knowledge to operate. These new systems are also smaller, which makes them perfect for real-time monitoring of bioprocesses both in-line and on-line, as well as for at-line and off-line measurements, opening up the technology to more applications and facilities. When combined with data science tools, Raman analysis can help manufacturers gain precise control over their processes by monitoring relevant parameters such as glucose, lactate, glutamine and glutamate, amino acids, pH, cell viability, and cell volume. Ultimately, this will enable higher yield and quality of the end product, while minimizing waste and reducing costs.

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Coping with Matrix Effects Caused by Phospholipids in Biological Samples

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Many scientists doing bioanalysis in the pharmaceutical industry use protein precipitation to clean up samples prior to analysis of small molecule drugs by LC-MS/MS. While this technique removes proteins quickly and inexpensively, it does not address the issue of ion suppression caused by phospholipids, which are present in biological sample matrices such as serum, plasma, and whole blood. During chromatography, coelution of phospholipids with the analyte of interest results in ion suppression and thus a decrease of mass spec signal that can cause variability and impact accuracy in quantitation. If the phospholipids do not immediately coelute with the analyte of interest, they can accumulate on the analytical column and elute later, unpredictably, during downstream analyses.

Ballistic gradients and small particles amplify the issue

Advances in LC-MS technology have allowed analysts to decrease LC run times by using ballistic HPLC gradients and columns with particles sizes of 2 µm or less. However, ballistic gradients often do not purge the column well enough of phospholipids that remain after typical protein precipitation protocols, and HPLC columns with small particles are generally more prone to clogging than ones with larger particles. Because contaminant phospholipids are often highly retained on the analytical column, they can take a prolonged period to elute. With the shorter run times however, phospholipids can accumulate on the column unless the analyst also adds a long column washing step. This added step can decrease laboratory throughput.

Traditional SPE versus chemical filtration

One approach to overcome the problem is to use traditional solid phase extraction (SPE). These methods are often based on a hydrophobic retention mechanism to separate the phospholipids from the sample's analyte of interest. This mechanism, however, leads to problems if the analyte is also hydrophobic. Such compounds are removed along with the hydrophobic phospholipids, which decreases analyte recovery and makes results inaccurate. These methods also often require time-consuming and analyte-dependent method development while still only removing nominal amounts of phospholipids. Remaining phospholipids can still accumulate on the analytical column and thus impact future analyses, add to column replacement costs, and increase instrument downtime. This problem led to the development of a new approach to phospholipid removal. Unlike with traditional SPE, where the analyte is retained on the sorbent through a washing step, the new approach utilizes a type of chemical filtration that selectively removes undesired phospholipids while allowing analytes to pass through unretained. This method is performed from the same high organic solvent composition, typically acetonitrile, that is used to precipitate the proteins. A variety of products designed specifically for the removal of both proteins and phospholipids have become commercially available. The stationary phase is typically packed into syringe-shaped cartridges, 96-well microtiter plates, flat disks, or pipette tip microextraction devices for small sample volumes. Most of these products use standardized, simple, and fast procedures requiring little method development.

How it works

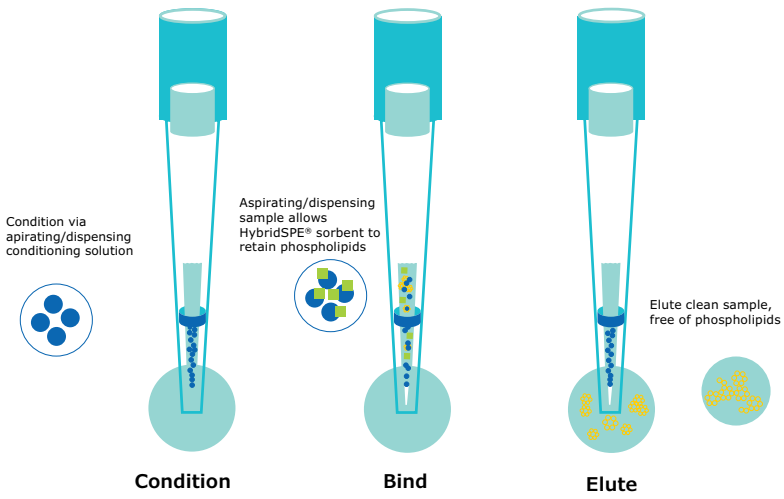
A technology introduced in recent years offers a means of removing phospholipids from a high organic solvent "protein crash" while allowing analytes to pass through, in essence a kind of chemical filtration. HybridSPE®-Phospholipid combines the simple, standardized methodology of traditional protein precipitation in an SPE

format for simultaneous removal of proteins and phospholipids from biological samples. Unlike phospholipid removal products that use a hydrophobic retention mechanism, the technology is based on zirconia (ZrO_2) coated onto the silica stationary phase. The zirconium (Zr) atoms act as a Lewis acid (electron acceptor), having empty d orbitals, while the phosphate moieties of phospholipids act as a strong Lewis base (electron donor). This mechansim provides for strong interaction between the phospholipids and the Zr atoms. The technology is capable of separating phospholipids from even highly hydrophobic analytes.

A diverse list of challenging analytes

Recently, we have placed the same HybridSPE® sorbent we use in common SPE formats into a Dispersive Pipette Extraction (DPX) tip format. The HybridSPE®-DPX tips are available in a variety of tip types for use with manual, semi-automated or fully automated liquid handlers. In this case, the sorbent is allowed to disperse and mix freely within the sample solution (Figure 1). Using it, applications have been developed for analysis of a range of challenging analytes. These analytes include clenbuterol, warfarin, verapamil, steroid hormones, omeprazole, digoxin, as well as antineoplastic, antidepressant, antiarrhythmic and immunosuppressant drugs. A further example is segesterone acetate (Nestorone®), a synthetic progestin for female and male contraception. The compound was previously measured in serum by radioimmunoassay but had non-specific interferences which led to erroneous, false-positive levels being reported in men. HybridSPE® DPX Tips allowed a sensitive LC-MS/MS assay for segesterone acetate in human serum to be developed and validated for use in clinical and research studies.

FIGURE 1. Workflow for using HybridSPE®-DPX tips.



To find out more about HybridSPE®-Phospholipid to remove phospholipids from biological samples, visit **sigmaaldrich.com/hybridSPE**

See applications in the MilliporeSigma chromatogram database for which HybridSPE® technology was successfully used: **sigmaaldrich.com/hybridspeProtocol**

Digital Transformation 101:

The "Swarm" approach

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Abstract

While data science is attracting significant industry interest, actual delivery does not always live up to its promises. A successful digital transformation strategy relies on changing attitudes and mindsets as one of its key aspects. This article shows how to accelerate cultural change towards data science-driven thinking in pharmaceutical companies. Literature best practice is followed by the personal experience of the authors. Specifically, we describe our "Swarm" philosophy to deliver many small, quick projects in a bottom-up fashion. This principle supports managed culture change starting at the shop floor, and relies on communication, collaboration and a focus on concrete value. Several supporting frameworks and tools are outlined. Further, we give an overview of our portfolio of projects, illustrated with two hands-on detailed examples. Our key learnings are articulated along the following three dimensions: strategy; people; and projects. This article illustrates the importance of combining agility with rigor, as well as that of a locally embedded resource to demonstrate value quickly.

Introduction

Nowadays, the digital transformation (DT), including data science, is an omnipresent topic with high business expectations.[1,2] At the World Economic Forum 2016, the value of digital transformation over the next 10 years was estimated to exceed the striking amount of $100T.[1] The success of DT has been demonstrated by the notable rise of today's giant digital corporations, albeit accompanied by concerns regarding power, privacy and taxation.[3] Industry shows strong interest in the extension of the digital transformation to completely new product and business models, leading to a fourth industrial revolution: Industry 4.0.[4] While many pharmaceutical companies strive for competitiveness by adopting Industry 4.0 concepts in decision automation,[4,5] many other such companies struggle to implement its precursor, the digital transformation for automation and the digitization of processes.[4,5] Furthermore, actual results from digital transformation efforts often fail to live up to their promises.[6,7,8]

Digitalization is a multi-faceted and diffuse topic.[6] Business strategies must therefore include many dimensions[3] to ensure successful incorporation and internalization of Industry 4.0 concepts[9] whilst establishing digital cultures and new capabilities.[2,10] Instead of merely solving unconnected business problems with customized technical and organizational solutions,[12] digitally maturing companies should focus on strategy development, mobilization for engagement, and project delivery.[3,11] A deep topic understanding is essential to set up an empowered and skilled team in order to build a strategy that focuses on actual, value-creating needs. The organization is mobilized by consistently investing in employee capabilities and by a managed cultural change towards cross-functional collaborations. Successful project delivery can be facilitated by a diversified portfolio and conscious decision-making.[3]

It is well recognized that a successful DT strategy stands and falls with changing the attitudes and mindsets of employees.[2,7,9,12] Especially in conservative companies, the full impact potential of advanced digitalization is often not recognized,[13] resulting in resistance to IT change, and decision-making based on wrongly perceived risks.[10] To speed up innovation,[10] digitally successful companies have accepted higher risks.[11] Furthermore, in companies embracing DT, a collaborative culture forms including natural- and data-scientists.[3] The mutual understanding between people of different backgrounds facilitates creativity and innovation.[11] To achieve the aims above, companies must invest into business structures and processes that accelerate cultural change towards data science driven thinking.

Here, we share the experience and insights gained during the past three years setting up our "Swarm" approach to demonstrate the value and applicability of DT to a community through many small, quick projects.

Gathering Support

Literature best practice

The adoption of "digital" constitutes a major shift from long-standing norms, thus challenging traditional hierarchies, decision-making authority, and workplace social interactions.[14] Such a cultural change requires getting people on board, as this change itself is driven by their ideas and engagement. The most critical component is joint project work between digital experts and members of the general community to raise mutual understanding and appreciation of each community's strengths, weaknesses, needs, and applicability.[2,10,15] The resulting exchange builds both a common language and knowledge base in data science, as well as a business and engineering context. Such activities are easier when the experts are embedded in the operational functions.

Additional training programs and educational resources can enhance the offering.[15] Additionally, regular digital summits help everyone feel involved and updated, while collaboration awards encourage participation,[14] and job rotation programs enable new perspectives.[14] Work environments can be set up in a way to foster engagement[11] and stimulate innovation through an inspiring and futuristic ambiance.[14]

Other game-changers in culture transformation include promoting new ways of working, such as autonomous judgment calls, and on-the-spot decisions,[14] for instance by setting incentives for their exploration.[10] To make risk-taking a cultural norm, business leaders have to embrace failure[11] and support employees in developing the necessary self-esteem and judgment skills. Leaders must serve as DT role models and consistently exemplify the novel behaviors so that motivated people follow their lead.[14] Throughout the transformation, people's drivers and resistances must be understood.

Implementation in our department

In the past experience of one author (P.M.P.), one cause for slow acceptance of DT was excessive focus on top-down corporate strategies. At the shop floor, these were perceived as too remote from daily concerns, both in content and accessibility. To increase interest and acceptance of DT in our own department, an intern position was therefore funded in 2020. It was framed as a scientific hypothesis: a test of the value of embedding a data science/IT worker in a physical science environment to implement a variety of digital solutions. The approach was successful and the internships have continued every year since 2020.

The "Swarm" Principle

Organizational context

The Pharmaceutical R&D (PTDC-F) department is part of the small molecules CMC (Chemistry, Manufacturing, Controls) division at F. Hoffmann-La Roche. Specifically, the department is responsible for formulation and process development of solid dosage forms, clinical trial materials manufacture, and internal/external technical transfer to commercial production. The division launched a formal DT initiative in 2019. It includes formally resourced division-scale activities for infrastructure development (such as the setup of a central data lake or data harmonization and integration), as well as various activity streams targeting data use.

For a successful culture change, however, this necessary top-down effort must be complemented by quickly helping many people with small requests. Our "Swarm" principle (Figure 1) is a bottom-up approach, where projects are led by internally embedded data scientists. These iteratively develop prototypes through continuous partner engagement with science or business subject matter experts from the department. This principle enables data scientists to deliver a large number, a "swarm," of small- to medium-scale collaborative projects, with fast response times due to low overhead. As applications mature and grow in complexity, a progressive handover process to permanent staff ensures long-term maintenance. The "Swarm" principle accelerates culture change by demonstrating early yet tangible value delivery to a number of department members, thus raising general awareness and interest.

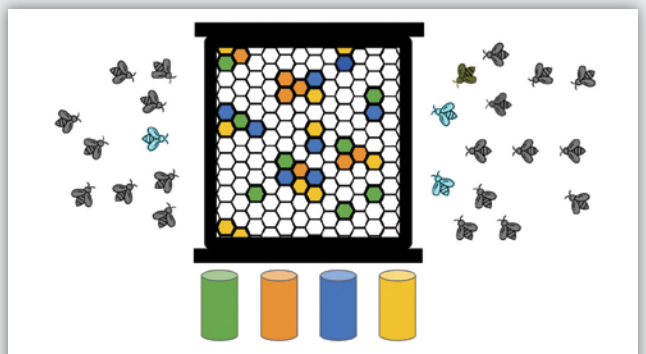


Figure 1. Visualization of the "Swarm" principle. Division-scale infrastructure development (represented as pillars) serve as the basis for the individual projects realized in the company (depicted as colored patches in the bee hive). Data Scientists (bright blue bees) work as a swarm in collaboration with natural scientists (gray bees) on short iterative projects to show a fast benefit to partners.

Historical perspective and strategy development

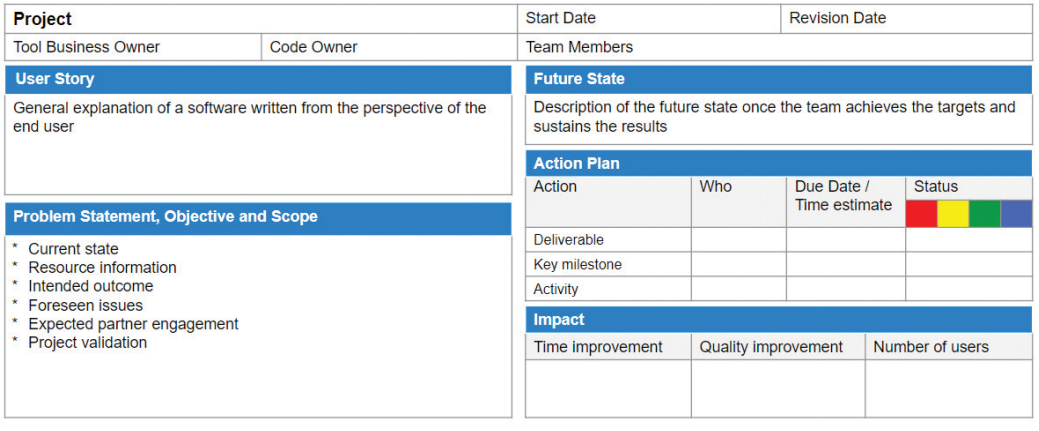
The first internship focused on the assembly of a portfolio of potential projects, together with its associated project management machinery. It identified sufficient numbers of valuable opportunities even just in our Sciences section. The delivery grew further the following year, raising connections and interest across the department, and producing quite a few useful tools. With the increase of the department maturity, more usage cases and project ideas from other sections appeared. By the third year, these successes had generated a very diverse set of projects in terms of subjects, partners and impact areas. More formal consideration became necessary regarding tool embedding into the data flow, their maintenance, and handover, leading to stronger collaborations with the division's growing community of data scientists. Further connection of top-down and bottom-up approaches will be crucial in the future to integrate small-scale projects in larger DT visions, and to better tailor division-wide solutions to end-users.

Supporting frameworks

We have developed many useful supporting frameworks to apply our "Swarm" principle effectively (Table 1).

Table 1. Overview of supporting frameworks, their purpose and contents.

Supporting framework	Purpose	Content
Project charter	Facilitate project scoping	• Project description including tool business and code owners • Users' stories • Scoping and project objective including current state, resources, intended outcomes, foreseen issues and project validation techniques • Future project state, maintenance • Action plan including project tasks, timelines and expected partner engagement • Value statements with quality and time improvements, number of users
Portfolio data table	• Track project progress • Support resource allocation • Enable portfolio analysis	• Project progress, resource, priority and urgency estimations • Software used, main activities, tool philosophy, quality and time improvements, number of users
Project documentation	• Facilitate project handover and error troubleshooting • Serve as user guidance	• Description of end product functionalities, testing, implementation strategy and problems that occurred • All relevant project links, the project charter, definition of code and tool business owner • Supporting best practice documents and user manuals



Project		Start Date	Revision Date
Tool Business Owner	Code Owner	Team Members	

User Story

General explanation of a software written from the perspective of the end user

Problem Statement, Objective and Scope

* Current state
* Resource information
* Intended outcome
* Foreseen issues
* Expected partner engagement
* Project validation

Future State

Description of the future state once the team achieves the targets and sustains the results

Action Plan

Action	Who	Due Date / Time estimate	Status
Deliverable			
Key milestone			
Activity			

Impact

Time improvement	Quality improvement	Number of users

Figure 2. Example project charter, used from the project scoping stage onwards.

- A simple, 1-slide, **project charter**[16,17] (Figure 2) to set common expectations and define intended outcomes. This is written in collaboration with all project partners after the first few meetings. Dividing projects into work packages simplifies project scoping and timeline setting. The charters are refined during the project execution.
- A **project portfolio table**[18] to manage each internship. These simple Google Sheets™ or Excel™ lists contain project essential information to track progress, allocate resources, and summarize descriptive project charter information. They facilitate portfolio analyses (see Table 1), including changes over the years, and value demonstration to the department.
- **Software solutions which enable real-time visual development** during prototyping (e.g. Google Data Studio™). These enable a critical capability: quick, functional, mock-up generation and concept testing, regardless of the final deployment platform.
- Comprehensive **project documentation** including developer records, handover documents, best practice documents, and user manuals. To facilitate project handover and troubleshooting, these must be started parallel to development and regularly revised.

Project Insights and Examples

This section starts by illustrating our approach with two hands-on detailed examples, one scientific and one business problem. This is followed by the insights from the analysis of the entire portfolio over the past three years.

Scientific example: Punch sticking

Punch sticking is a phenomenon that can pose severe problems in tablet manufacturing. It refers to strong adherence of powder onto the tablet tooling, which can lead to significant tablet surface defects and productivity losses.[19,20] This problem is often only identified late in development, when formulation changes carry severe time and money penalties.[20] As an early test, Roche utilizes a small-scale removable punch sticking assay to quantify the amount of material adhered to the tablet tooling after a small number of compactions. Prior to our work, the data was collected in various Excel™ sheets on different file-sharing platforms. Risk classifications were made based only on the measurement at the highest number of compactions.

Together with our formulators, we developed an R Shiny™ application to enable access to the consolidated data from one communal place, and to classify formulations more robustly in terms of their sticking risk at manufacturing scale. The Shiny application consists of one main sidebar tab for each of these use cases. The *Data Viewer* tab (Figure 3A) lets the user access the previous data from one data-combining Google Sheet™ via a Google service account and explore various plots quantifying the sticking propensity of selected formulations. In the *Data Prediction* tab, the user can enter new measurements, and add them to the database. Furthermore, the sticking behavior of the corresponding formulation can be predicted through data fitting to a slightly adapted version of the function by (Paul et al, 2016).[21] The mass sticking after a customizable number of compressions is calculated together with bootstrap confidence intervals and a risk classification (Figure 3B). Explanatory text helps the user interpret the prediction outputs, including summary statistics on model fit. This text warns in case of high sticking risk, or insufficient model fit, e.g., due to large experimental noise. Finally, to facilitate reporting, a PDF report containing all plots and summary statistics shown in the app can be automatically generated.

Currently, the application is utilized to provide guidance in early development. The prediction and risk classification will be continuously optimized with future validation data as part of the model life-cycle management.

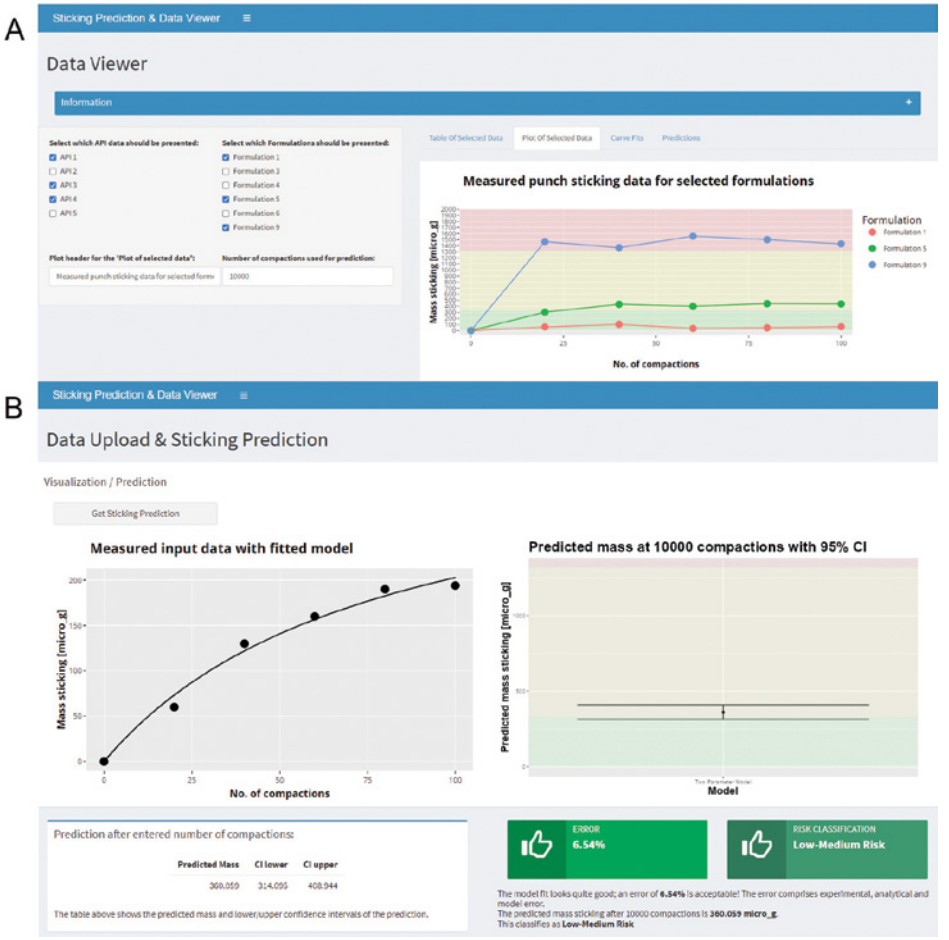


Figure 3. Screenshots from the Sticking Application. A: Data Viewer showing measurements of selected formulations. B: Data Prediction for newly entered data with function fit, predicted value including bootstrap confidence intervals, error and risk classification, as well as explanatory text of the outcome.

Business example: DT Dashboard

During the past years, increased transparency on several department activities has been requested, so we have worked on various dashboards. In particular, the workstreams, efforts and achievements of the department's DT initiative itself needed better dissemination to enhance team collaboration. We thus developed a DT dashboard in Google Data Studio™ to make all the information accessible and traceable in an easy and quick way. It automatically synchronizes detailed project information recorded in a Smartsheet™ with the dashboard embedded in the department Google Site™.

The DT dashboard is composed of five main pages that provide an overview of ongoing and planned DT projects within PTDC-F (Figure 4). The pages, easily accessible through the department intranet homepage (Figure 4A), show full-time equivalent (FTE) spending per project, as well as detailed timelines of bigger projects and initiatives like our equipment integration (not shown). The dashboard contains interactive graphs like the percentage of different features (tasks) in individual epics (projects), which in Figure 5B shows us the projects in the initiative data consumption and how big (in terms of tasks) each project is. Furthermore, the graphics are fully interactive, e.g., by clicking on the pie chart slices, links for the relevant DT solutions are displayed in the table below the chart (Figure 4B). One can also examine the status of each task, here equipment connection to the server per piece of equipment (Figure 4C). Similar to Figure 4B, the table in Figure 4C interactively displays timelines for the equipment selected via mouse clicking on the plot. This dashboard was presented in a departmental meeting to make DT progress accessible to all PTDC-F employees.

Portfolio analysis

Over three years, 40 projects were completed with 20 main project partners. The project content was highly diverse, ranging from website and model development to database management. Two constant needs were process automation (8-44% of projects per year) and data communication through visualizations or spreadsheets (25-37%

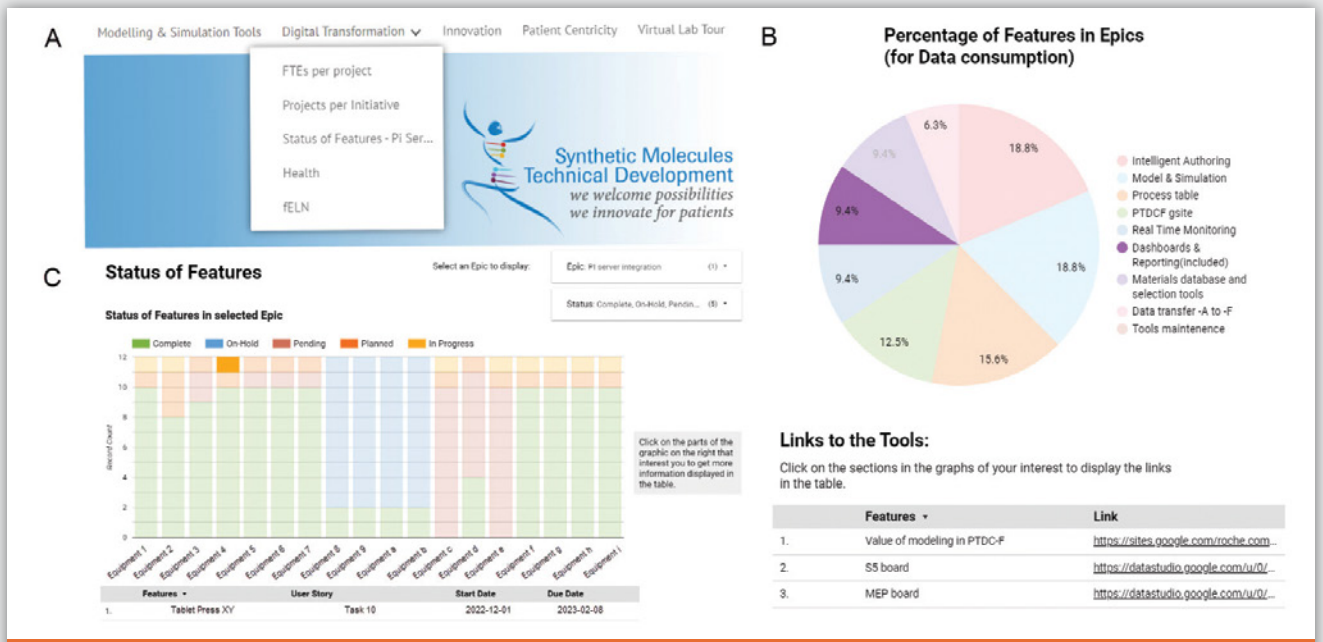


Figure 4. Screenshots of the DT Dashboard on the PTDC-F homepage. A: Embedding of the individual dashboard pages into the department website. B: Interactive dashboard plot showing the percentage of different features (tasks) in individual epics (projects) in the 'data consumption' initiative. The table below the pie chart displays links to the corresponding tools. C: Status of different features for the epic 'PI Server Integration', also interactively linked with the table below.

and 11-33% respectively). Due to this diversity, various software had to be utilized (Figure 5A). We concluded that generalists with strong knowledge in R™ and Python™ programming, but also visualization, data handling and problem-solving skills suited our embedded positions best. In terms of their philosophy,[15] the tools developed were mostly used for descriptive analysis (42-67% of projects per year), but query and predictive analysis also constituted many projects every year (17-26% and 11-21%). The focus on intermediate complexity of interpretation reflects that DT is neither at its start nor completely mature in our department. The projects added value in many different ways (Figure 5B). The main benefits[21] are productivity, team collaboration and traceability, which together make up 50-67% of the total project efforts each year.

Over the years, the percentage of projects realized specifically for the Sciences section housing the interns strongly decreased (Figure 5C). Correspondingly, there was a continuous increase in the percentage of projects on department (PTDC-F) or division wide scale (PTDC), showing the success of the activity. Since the tools were developed for a broader community, there were higher user numbers per project in the last year. Where in the first two years all projects were designed for <50 people, in the following year 32% of the tools were intended for 50-99 users and even 15% for >100 people. The time savings per user were quite low for the first year's projects, since it included much valuable prototyping. These savings increased in the following years since tools for more concrete use cases were developed.

Altogether, the three generations of interns successfully delivered a manifold of value to a broad spectrum of people. The results demonstrate the diversity of opportunities available for DT tools in our Pharmaceutical R&D environment, and the increasing department interest in data science activities.

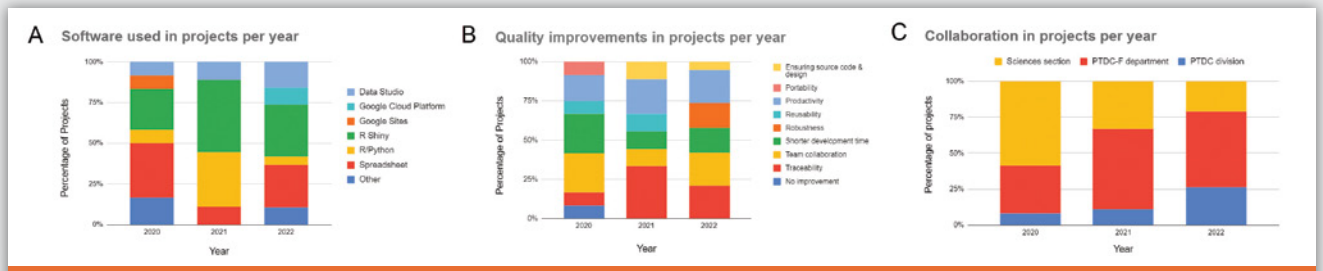


Figure 5. Portfolio analysis of projects led by the interns (V.L., K.L., J.P.). A: Software usage in projects per year. B: Quality improvement in projects per year. C: Collaboration in projects per year.

Learnings

In the following few paragraphs, our key learnings are articulated along the following three dimensions:[3] strategy; people; and projects, including their delivery.

Strategy

To explore new areas, calculated risks must be taken: in our case, the funding of the first embedded data science internship. In its context, the creation of a starting portfolio was very important. This assembly showed the needs of the department, as well as the skill sets required; in addition, it secured buy-in from a variety of colleagues. We then patiently focused on collaboratively fulfilling real needs together with the beneficiaries. As the first projects were successfully delivered, the whole approach acquired legitimacy. The expansion to a larger, diversified portfolio with many different project partners must be progressive to avoid spreading the effort and focus too thin. This strategy showed success over time across the whole department.

People

A major focus area was the tight integration of the data scientist in the department to improve bilateral understanding and identification of business needs, as well as to facilitate communication in ongoing projects. Finding a common language between project partners and abstracting the discussions to the level of detail needed was crucial. We managed culture change by designing a variety of communication channels over the last three years. The data science activities thus became well recognized in the department, and interest in the initiation of new projects, as well as tool maintenance, increased a lot. We learned that it is crucial to strengthen also the informal interaction between data and natural scientists, as a key success factor to a successful "Swarm" approach is the presence of open mindsets inside the department that bring in ideas and contribute to the change of the entire organization.

Project/delivery

Agreeing on a clear project scope is a critical step for a successful project delivery. We ensured clarity through project charters and up-front definition of work packages. To provide efficiency, but also robustness, it is important to work in ways consistent with the organization. Input gathering from other data scientists before starting with the exact implementation gives options to adapt or integrate into previously developed solutions, and ensures consistent data formatting. We found scheduling regular check-ins with project partners useful to involve them in the iterative development process and ensured that expectations were met. Furthermore, user-friendly, highly visual tools with pre-interpreted results and interactive features are most easily accepted. In summary, the overall key to success is sufficient planning effort, followed by fast prototyping and iterative, co-creative development with parallel testing.

Conclusion

A successful digital transformation strategy comprises both bigger top-down activities and emerging bottom-up projects. Our experience shows that the latter are essential drivers to culture change. We introduced the "Swarm" principle as a bottom-up approach designed to maximize buy-in, by demonstrating early yet tangible value throughout an organization in an agile manner.

The "Swarm" principle relies on local data scientists embedded in operational functions to increase the bilateral understanding of business needs and thus deliver many small collaborative projects. Project management success factors are simplicity and efficiency, facilitated by 1-slide project charters, good breakdown into work packages, and living project documentation. The assembly and analysis of a varied project portfolio ensured a strategic outlook.

As summarized in the previous section, our experiences have taught us many lessons that will apply to other organizations in their own DT journeys. Culture change requires patience and persistence, as well as the commitment to continually deliver value to numerous partners. Together with a collaborative approach and a focus on user-friendly, interpretable tools, we are confident these elements will be helpful to any DT champions.

The increase in the number of people engaging with the DT over the years in our department demonstrates the high efficacy of the "Swarm" approach in culture change. Our principle has also led to individual personal development for us, thanks to different directions we have sought to foster DT in. It can do so for the readers of this article as well. As they search to identify the best opportunities to harness the power of machines to human and societal questions, the words of Cordwainer Smith still hold true: "There is no all-purpose computer built that weighs as little as a hundred and fifty pounds. You do."[22]

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Author Biographies

Jennifer Probst *is a Masters student in Computational Biology and Bioinformatics at ETH Zurich, Switzerland. Alongside her studies, she has contributed as data scientist to several global research projects; including LAMAVE, Archipelagos Institute of Marine Conservation, the University of Zurich and Hawk Mountain Sanctuary Association. The past nine months she has been working as data science intern in the Formulation & Process Sciences section at Roche in support of the Digital Transformation initiative.*

Kevin Ly *is a bioinformatics Ph.D. student at the Wellcome Sanger Institute affiliated to the University of Cambridge. During two years at Roche, he contributed to the Digital Transformation in the Pharma Technical Development; first as a data science intern in the Formulation & Process Sciences section and subsequently as a data science engineer in the Real-Time Monitoring team. In his roles, he automated manual analytical processes by streamlining data pipelines and incorporating data science tools.*

Valentin Legras *is a clinical pharmacology data scientist at Roche in Basel, Switzerland. After spending some years with Sanofi and Novartis, he joined Roche in 2020 as the first data science intern in the pharma technical development department. In support of the digital transformation, he mainly worked on databases, data reporting, automation and digitalization of the tools. Currently, he focuses on pharmacokinetic and pharmacodynamics clinical data, data reporting and data preparation.*

Avinash Murthy *is a senior scientist at Roche in Basel. He joined Roche in 2014 after obtaining a Ph.D. in Chemical Engineering from the University of Texas at Austin. During his almost nine years at Roche, he has worked on various drug development programs in drug product formulation and process development, with a particular focus on late-stage development. Recently he has become the process development squad lead within the department.*

Ana Filipa Borges *is a senior scientist at Roche in Basel. Her background is in Pharmaceutical Sciences but she specialized in Pharmaceutical Technology during her Ph.D. She spent five years at Bluepharma Group's innovation unit developing new dosage form platforms for oral delivery, followed by two years in PCI Pharma and two years in Novartis as Product Formulation Lead. After 2.5 years as Senior Scientist in Roche, she has had the opportunity to follow product development from the scratch to the market, and become the Digital Transformation lead within the department.*

Dr. Patrick M. Piccione *is a senior principal scientist at Roche in Basel. He spent seven years in materials development at Arkema, followed by nine years at Syngenta. There he led process engineering science, as well as a "maths & data science" initiative. Over the last 3.5 years, he has acted as the Pharmaceutical R&D department's sponsor for the Digital Transformation. As such, he oversaw the creation of a variety of IT & data science tools through the internship program described here. He is now setting up a modeling and simulation squad across the entire CMC division.*

Potential of Gene and Cell Therapies for Patients with Rare/Orphan Diseases, Ensuring Access to Treatment

Andy Szczotka, PharmD

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AscellaHealth

For the estimated 25-30 million Americans[1] and 400 million people worldwide[2] living with a rare disease, news of potential new gene therapies is a powerful message that resonates personally among individuals and families. Approximately 80% of rare diseases are caused by a single-gene defect in a person's genes,[3] and unfortunately, rare diseases often are difficult to diagnose, with few or no treatment options available. In fact, it is estimated that 95% of rare diseases do not yet have a single FDA-approved treatment.[3] and rare diseases impact more people than cancer and AIDS combined.[3]

According to the U.S. Food & Drug Administration (FDA), gene therapy is a technique[4] that modifies a person's genes to treat or cure disease. Gene therapy (GT) is the process of replacing defective genes with healthy ones, adding new genes to help the body fight or treat disease, or turn off genes that are causing problems.

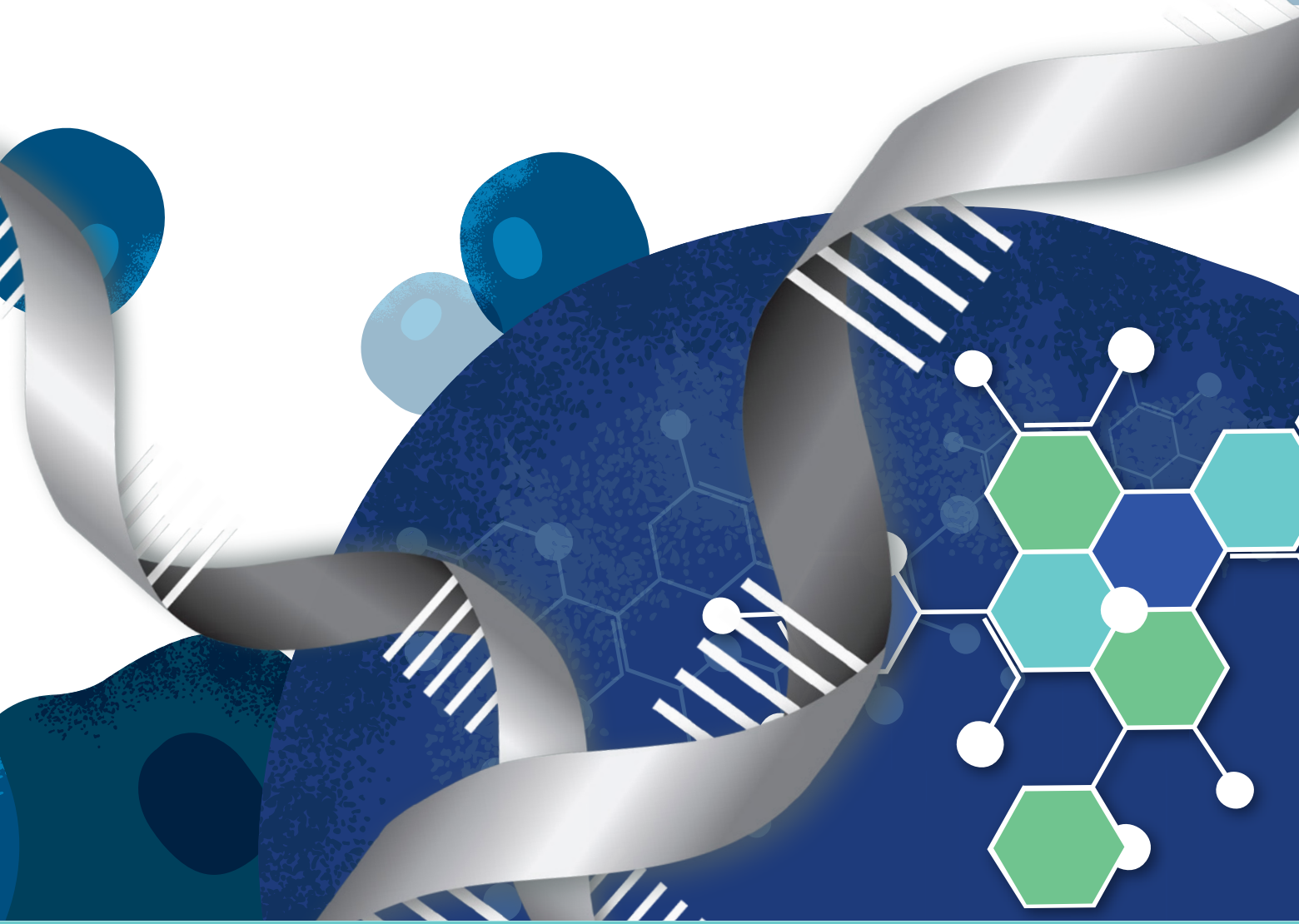
Gene therapies use a target gene that expresses protein products at a sufficient level to cure, or at least ameliorate, a disease caused by a genetic defect. This involves the transfer of genetic material, usually in a carrier or vector, and the uptake of the gene into the appropriate cells of the body. Cell therapy also has the potential to treat the inherent cause of both genetic and acquired diseases but involves the transfer of cells with the relevant function into the patient.

Both approaches have the potential to alleviate the underlying causes[5] by replacing the missing protein(s) or cells causing the disease symptoms, suppressing expression of proteins which are toxic to cells, or eliminating cancerous cells. Many different types of cells[6] may be used as part of a therapy or treatment for a variety of diseases and conditions, including hematopoietic (blood-forming) stem cells (HSC), skeletal muscle stem cells, mesenchymal stem cells, lymphocytes, dendritic cells, and pancreatic islet cells.

As of this writing, below is a list of licensed products from the Office of Tissues and Advanced Therapies (OTAT), alphabetical by brand name and uses:[7]

Industry-leading Modified NTPs for mRNA production

Now Available: GMP-Grade N1-methylpseudouridine-5’-triphosphate



Ver. 09.15.2022

Leading the Way in mRNA™

TriLink BIOTECHNOLOGIES
part of Maravai LifeSciences

ABECMA (idecabtagene vicleucel)

Multiple Myeloma

ALLOCORD (HPC, Cord Blood)

SSM Cardinal Glennon Children's Medical Center

BREYANZI

B-cell lymphoma

CARVYKTI (ciltacabtagene autoleucel)

Janssen Biotech, Inc.

CLEVECORD (HPC Cord Blood)

Disorders affecting the hematopoietic system

Ducord, HPC Cord Blood

Disorders affecting the hematopoietic system

GINTUIT (Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen)

Treatment of mucogingival condition

HEMACORD (HPC, cord blood)

Disorders affecting the hematopoietic system

HPC, Cord Blood

Disorders affecting the hematopoietic system

HPC, Cord Blood - MD Anderson Cord Blood Bank

Disorders affecting the hematopoietic system

HPC, Cord Blood - LifeSouth

Disorders affecting the hematopoietic system

HPC, Cord Blood - Bloodworks

Disorders affecting the hematopoietic system

IMLYGIC (talimogene laherparepvec)

Melanoma

KYMRIAH (tisagenlecleucel)

Acute Lymphoblastic Leukemia & B cell lymphoma

LAVIV (Azficel-T)

Nasolabial fold wrinkles

LUXTURNA

Retinal dystrophy

MACI (Autologous Cultured Chondrocytes on a Porcine Collagen Membrane)

Autologous Cultured Chondrocytes on a Porcine Collagen Membrane
PROVENGE (sipuleucel-T)

Prostate Cancer

RETHYMIC

Congenital athymia

SKYSONA (elivaldogene autotemcel)

Active cerebral adrenoleukodystrophy (CALD).

STRATAGRAFT

Allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen

TECARTUS (brexucabtagene autoleucel)

Acute Lymphoblastic Leukemia & Mantle Cell Lymphoma

YESCARTA (axicabtagene ciloleucel)

Follicular Lymphoma & B cell lymphoma

ZYNTEGLO (betibeglogene autotemcel)

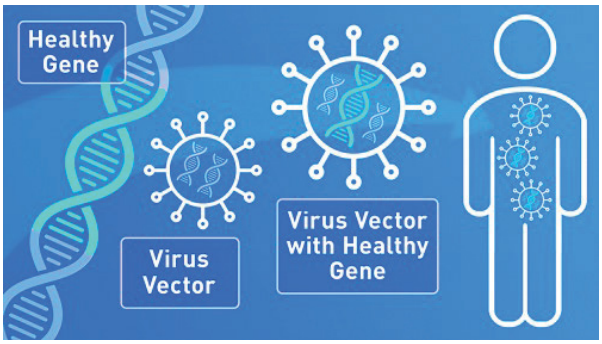
ß-thalassemia

ZOLGENSMA (onasemnogene abeparvovec-xioi)

Spinal Muscular Atrophy

A Lexicon for Main Types of Gene Therapy Products

Viral Vectors is the term that the FDA uses when referring to viruses that are modified to remove their ability to cause infectious disease. Viruses have a natural ability to deliver genetic material into cells, and therefore some gene therapy products are derived from viruses.[8] These modified viruses can be used as vectors (vehicles) to carry therapeutic genes into human cells (Figure 1).

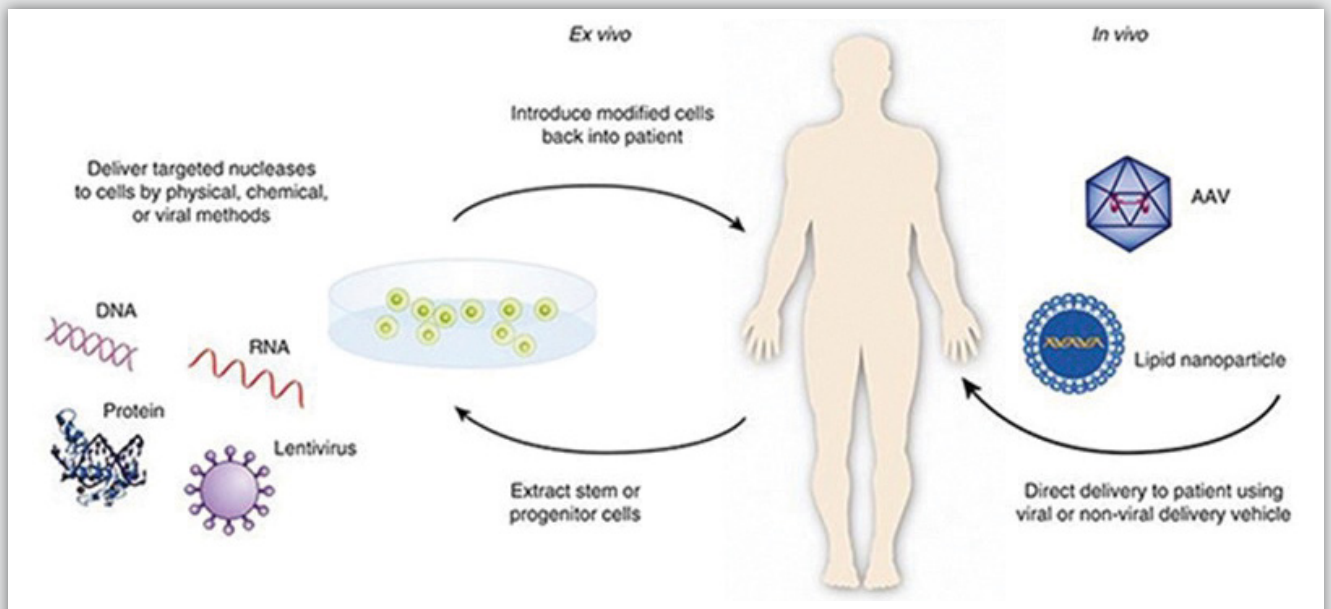


Source: Food & Drug Administration. https://www.fda.gov/consumers/consumer-updates/how-gene-therapy-can-cure-or-treat-diseases?%20how%20does%20it%20work?

Figure 1.

Patient-derived cellular gene therapies refer to products where cells are removed from the patient, genetically modified (often using a viral vector) and then returned to the patient.[6]

Plasmid DNA describes circular DNA molecules that can be genetically engineered to carry the good therapeutic genes into human cells.



Source: Food & Drug Administration. Available at https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy

Figure 2.

Bacteria can be modified to prevent them from causing infectious disease and then used as vectors (vehicles) to carry therapeutic genes into human tissues.

Human gene editing technology maintains a goal to disrupt harmful genes or to repair mutated genes.[6]

Two Categories of Gene Therapies

There are two main ways to deliver gene therapy: *ex vivo* and *in vivo* methods. The *in vivo* gene therapy approach as illustrated above (Figure 2) means that therapy is administered directly to the patient and the targeted cells remain in the body of the patient.[4] This methodology involves use of a gene inserted into a viral envelope, often an adeno-associated virus (AAV). The gene-carrying virus is prepared in a laboratory and delivered to the target organ either by an injection or a simple infusion, where it is taken up by cells in target organs. While it is not integrated into the chromosome, it does appear to have a sturdy and long-lasting response, especially in slowly replicating cells like retinal cells, or neurons. Luxturna and Zolgensma are examples of *in vivo* gene therapies.

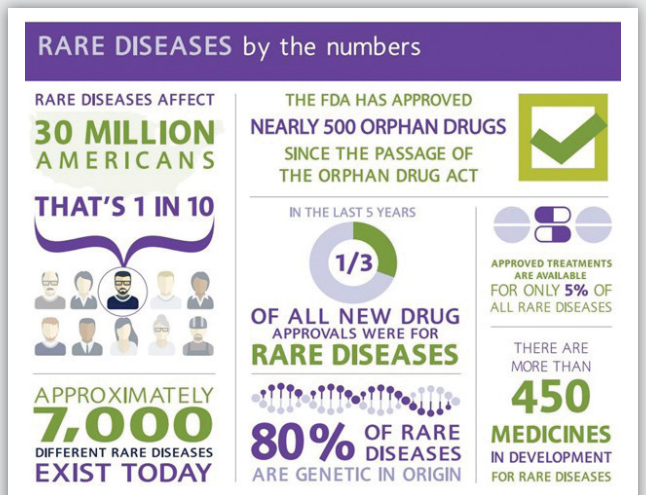
With the *ex vivo* approach, the targeted cells are removed from the patient and gene therapy is administered to the cells *in vitro* before they are returned to the patient's body. Target cells containing the faulty or missing genes are extracted from the patient in a clinical setting, such as the hospital, and the cells are re-engineered in the laboratory to integrate a new or functional gene into the chromosome. The reprogrammed cells are then infused into the patient and the new gene is distributed through the patient's system as these cells multiply.

Examples of the *ex vivo* approach are chimeric antigen receptor T-cell (CAR-T) therapies such as Abecma (idecabtagene vicleucel), Breyanzi (lisocabtagene maraleucel), Kymriah (tisagenlecleucel), Tecartus (brexucabtagene autoleucel) and Yescarta (axicabtagene ciloleucel).

Gene Therapy Issues, Challenges and Concerns

Gene and cell therapies are prime examples of hyper-innovation that is needed and will benefit people with rare diseases who have been sidelined for too long with little to no treatment options. In fact, many rare disease patients use drugs off-label based on limited data because they have no better options available (Figure 3). While these therapies offer hope and represent a revolutionary step forward in the potential treatment of many previously incurable diseases, they present huge affordability challenges and carry very exorbitant up-front costs with no cost-minimization, elimination guarantees or impact on quality of life. Multi-million dollar price tags are becoming more common, as the FDA recently approved Skysona[9] for a rare neurological disorder called cerebral adrenoleukodystrophy at a list price of $3 million.

Another concern is the longevity of response to the product, since it may be too early to tell how long the effects of the treatments will last: restored vision, disease remission or other may endure for a lifetime versus a specific time period. This is particularly problematic since



Source: PhRMA.org. A Decade of Innovation in Rare Diseases. Available at http://phrma-docs.phrma.org/sites/default/files/pdf/PhRMA-Decade-of-Innovation-Rare-Diseases.pdf

Figure 3.

there is currently minimal patient follow-up data to know whether these products will be cures or if the disease may return.

Adverse reactions are also a major issue, as serious adverse events[10] (AEs) associated with these therapies are garnering more attention and the mitigation of these AEs represent an unmet need in this emerging field.[11] This points to the need for recommendations regarding the design of long term follow-up studies[12] for the collection of data on delayed adverse events following administration of a GT product.

Furthermore, many clinical trials have been put on hold to evaluate adverse reactions amid troublesome reports[13] regarding the disadvantages to using the Adenovirus, the most commonly used vector in gene therapy clinical trials. Risks include non-integration, immunogenicity, replication competence, no targeting, and small insert size.

Other key areas of concern that include:

- Hepatotoxicity: liver damage
- Neurotoxicity: toxic substances alter normal activity of the nervous system.
- Various types of cancer including acute myeloid leukemia, often based upon animal models with tumor development.
- Autoimmune response: body attacks and damages its own tissues.
- Use in immunocompromised patients and viral load concerns: can mean the person is more infectious, such as breakthrough infections of COVID-19.

Specialty Pharmacy Optimizes Management of Gene Therapies

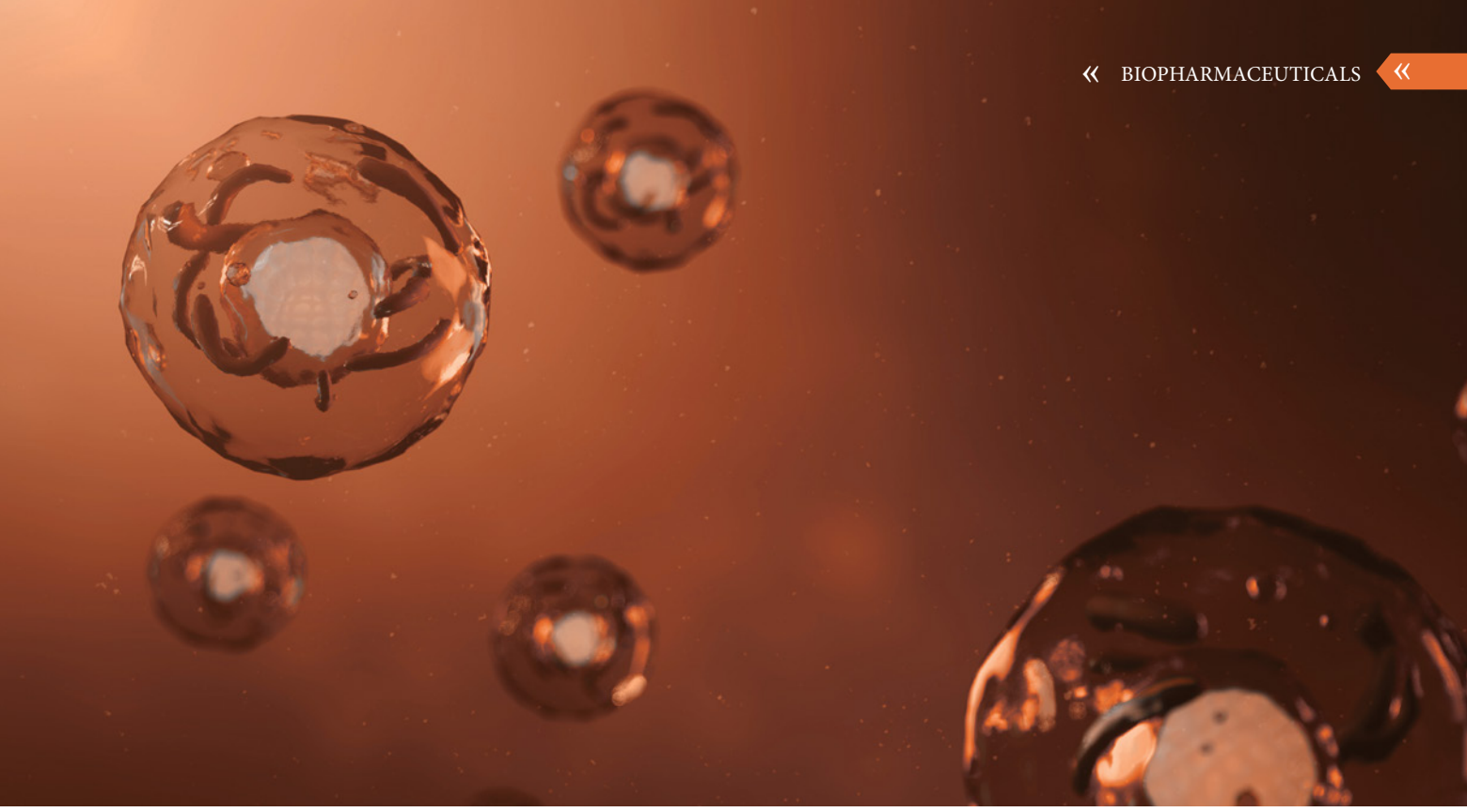
The evolving, critical role of Specialty Pharmacy (SP) in the management of gene therapies cannot be understated. Ideally, they maintain direct relationships with product manufacturers and offer end-to-end solutions to facilitate payment reimbursement, support processes and implement 'white glove' services with a high-touch patient centered model that is focused on patient outcomes. SPs that offer a full range of programs and services across the product lifecycle, from pre-commercialization and market access, distribution, fulfilment, and Hub services to compliance and monitoring for enhanced patient outcomes, are best positioned to fulfill manufacturer expectations for optimized product adoption, increased patient engagement and better outcomes as well as streamlined communications between prescriber, patient and pharmacy that decrease time to fill.

By employing a consultative approach to seamless new product launches that provide early insights into market conditions, as well as experienced teams to negotiate with payers, SPs ensure streamlined access to therapies and advantageous pricing. Progressive SPs are pioneering innovative technology-based suites of unique financial solutions, including loan-based programs for cell/gene therapies to help offset the high cost of curative medications and copay advisory services to monitor and track manufacturer copay funds, ensuring that allotted funds are utilized to help offset costs of expensive therapies for patients. This also includes alternative funding programs which means of access to philanthropic organizations, grants or other foundational programs that support access to high-cost therapies and shift the cost away from the patient and payer.

Utilization Management Approaches to Lower the Cost of Care

SPs apply programs such as step care therapy, quantity limits, partial fill programs and other initiatives to control costs. The development of criteria for prior authorization, for example, ensures appropriate use and enhances opportunity for positive outcomes. Typically, criteria is based upon clinical study inclusion and exclusion criteria, interpretation of clinical study endpoints, national guidelines and CMS/Medicare policies. Additional use of benefit maximum and deductible programs and application of rebate management programs impact the cost of care. Finally, by identifying alternative Site of Care programs, SPs can direct patients to lower cost sites of quality care that can provide cost savings to the patient and payer while making it more convenient for patients, caregivers and support team members to access care.

Cell and gene therapies are at the forefront of innovation and transforming how we treat certain diseases. Over the next few years, more than 50 new *in vivo* and *ex vivo* gene-therapy launches are already planned.[14] As the urgent need for research continues, with pharmaceutical companies continuing to map the genes responsible for rare diseases and develop gene and cell therapies, these manufacturers will want to identify and collaborate with the SP community for optimal product market access.



Manufacturers and other companies developing these therapies will play an instrumental role in working closely with the complex network of industry stakeholders to advance these therapies and ensure they are reaching those in need, which is the most progressive approach for clinical development and patient care. It is anticipated that these therapies will effectively address the struggles of millions of people and their families in the journey towards better health.

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About the Author

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FDA's Updated Inspectional Approach in the Post-Pandemic Landscape

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Introduction

The COVID-19 pandemic posed unprecedented challenges to the U.S. Food and Drug Administration's (FDA) inspection program. Emergency public health measures, including global travel restrictions and lockdowns, forced FDA to essentially suspend its inspection activities, creating a significant inspections backlog.[1] Both the pharmaceutical industry and Congress voiced concerns over the backlog and the potential ramifications for the American public. In response, FDA piloted new inspection techniques and strengthened its reliance on mutual recognition of inspections by international regulatory bodies.[2] Based on the relative success of these initiatives during the pandemic, FDA is now adopting them beyond the COVID-19 pandemic as "modernized approaches to protecting public health."[3]

FDA's Inspectional Authority

To protect consumers in the United States, FDA closely regulates pharmaceutical manufacturing, and in order to do so, the agency has broad statutory authority to physically inspect any factory, warehouse, or establishment in which drugs are manufactured, processed, packed, or held for introduction into U.S. commerce.[4] This authority allows the agency to inspect "all things," including "records, files, papers, processes, controls and facilities"[5] bearing on an establishment's compliance with current Good Manufacturing Practice (cGMP).[6] The authority to inspect in person extends not only to manufacturers located in the U.S., but to any site around the world that either manufactures drugs to the U.S. market or seeks approval to do so.[7] Among other things, onsite inspections permit FDA investigators to tour the facilities and laboratories to observe the day-to-day operating environment, conduct comprehensive reviews of manufacturing and quality records such as deviations and changes from the approved process, and directly interview factory employees regarding their cGMP compliance. The FDA investigators who perform the inspections are subject matter experts in a range of relevant areas (e.g., chemistry, microbiology, engineering, aseptic practices), and are specifically trained to identify manufacturing or quality deficiencies that can become serious problems if not corrected. As a result, FDA heavily relies upon its inspections to ensure that U.S. marketed drugs are safe and effective.

Inspections During the Pandemic

Although FDA has seen a general decline in domestic and foreign inspections since 2016 due to staffing vacancies,[8] the unprecedented obstacles posed by COVID-19 and the related public health measures triggered an extremely sharp drop in inspections.[9] Limitations on in-person contact due to the COVID-19 virus such as lockdowns and travel bans created substantial obstacles for investigators to continue inspecting facilities in person.[10] In March 2020, FDA announced it would temporarily halt foreign and domestic inspections other than those it deemed "mission critical."[11] Following this announcement, FDA only conducted three foreign inspections for the rest of the fiscal year, compared to hundreds more during the same time period in each of the prior two years.[12] This is especially noteworthy given that approximately 70 percent of facilities which manufacture active pharmaceutical ingredients and more than 50 percent of facilities which manufacture finished drugs for the U.S. market are located outside the U.S.[13] FDA's domestic inspections also decreased significantly.[14] And the decline in inspections continued through Fiscal Year 2021, creating a substantial backlog of thousands of inspections,[15] raising concerns from both public and private entities.[16]

The inability to inspect "remove[d] a critical source of information about the quality of drugs manufactured for the U.S. market," which raised warning bells.[17] In particular, members of Congress sent a letter to then-acting FDA Commissioner Janet Woodcock with questions about FDA's efforts to "mitigate the backlog of […] inspections."[18] Congress expressed "concern[…] that more than one year into the pandemic, the strategy for resuming all inspections and addressing the backlog of delayed inspections remains unclear."[19] The letter pressed FDA to resume onsite inspections and make improvements to its current inspectional techniques due to the extended time between inspections to "ensure patient access to safe and effective medicines."[20] Relatedly, FDA has also faced pressure from industry for increased inspections to ensure the continuous supply of necessary drugs in the United States.[21]

FDA's New Inspectional Approach and Techniques

In order to decrease the backlog of inspections and bolster assessments of foreign manufacturers, beginning in 2021, FDA modified its approach to inspections in three key ways: (1) conducting remote assessments, (2) sharing and relying upon information from international regulatory bodies, and (3) initiating unannounced inspections for foreign manufacturers.[22]

First, to continue its inspections during the pandemic, FDA piloted and increasingly relied on remote regulatory assessments (RRAs), which are reviews of records and other information submitted upon request from FDA.[23] The reviews are conducted entirely remotely, and the agency has frequently requested and assessed documents remotely during the COVID-19 pandemic. Records requests are mandatory since FDA is statutorily authorized to review documents remotely in advance or in lieu of onsite inspections.[24] Only establishments engaged in the manufacture, preparation, propagation, compounding, processing, or importation of a drug may be subject to mandatory RRAs. FDA also unveiled non-mandatory or voluntary assessments such as remote interactive evaluations using technologies such as livestreaming of video operations, teleconferences, and screensharing.[25] FDA plans to use these remote interactive evaluations to "verify corrective actions taken in response to inspections of previously compliant manufacturers and in gaining compliance insight."[26] The agency's recent draft guidance on RRAs provides helpful context for how it will conduct records reviews and remote interactive evaluations going forward, and notes the types of records that could be requested. These include test results, deviation and non-conformance reports,

process validation records, standard operating procedures, and product complaints, among many other examples.

FDA has stated it will use a risk-based approach to determine which establishments to initiate or request RRAs, considering "firm location, inspection history, complexity of product and process, and travel restrictions."[27] FDA has also begun factoring more up-to-date data from its quality metrics program and other sources in its risk-based inspection prioritization system since the pandemic.[28] Historically, FDA has relied only on facility scores (which consider factors such as type of establishment, number of products manufactured, and inspection history), product scores (which consider factors such as type of product, dosage form, and sterility), and time since last inspection in determining which sites to inspect.[29] Due to decreased resources and opportunities during the pandemic, FDA has sped up modifying its risk-based inspection scheduling model to incorporate risk scores that rely on additional quality metrics and other data, such as more precise facility types, geographical locations with higher compliance rates, recall and inspectional history, and results from inspections conducted by foreign regulators.[30]

Second, FDA began to increasingly rely on information and reports from international regulatory bodies. FDA is statutorily authorized to rely on information and observations collected by competent foreign regulatory authorities through mutual recognition.[31] While mutual recognition has existed in the U.S. since 2014 and for longer in the European Union, the agency rarely relied upon mutual recognition prior to the COVID-19 pandemic.[32] Mutual recognition provides regulators greater efficiency and allows agencies to synchronize inspection schedules and allocate sufficient resources toward higher risk inspections, without duplicating efforts. Because of these strategic benefits, FDA will likely continue to take into account inspections conducted by other international regulators, and companies should prepare for all inspections with the same level of readiness. The expansion of mutual recognition is part of FDA's larger goal to globalize its inspection program, by facilitating greater coordination and oversight of medical products among foreign regulatory bodies.[33] FDA believes that information sharing with competent foreign regulatory bodies will allow it to become "more efficient" and the "industry can implement innovations and quality systems in a more rapid and effective manner." Going forward, FDA is considering expanding the scope of mutual recognition with the UK and EU to include vaccines and plasma-derived pharmaceuticals.[34]

Third, FDA has begun conducting unannounced inspections of foreign manufacturers. Prior to the COVID-19 pandemic, facilities based outside of the U.S. were typically provided with advance notice of an upcoming inspection, sometimes as much as three months' time. FDA initially began performing unannounced foreign inspections during the pandemic following criticism from the industry that notice to international facilities can "harm an FDA inspector's ability to get transparent information about a company's standard operating practices."[35] A report from the U.S. Government Accountability Office ("GAO") noted the issue of establishments quickly fixing potentially serious problems prior to FDA inspections, and recommended that FDA should adopt a pilot plan for unannounced foreign inspections to ensure inspection integrity.[36] Arriving unannounced, particularly after the long the delays in time between inspections due to the pandemic, certainly bolsters the credibility of the foreign inspection program. In response, FDA has begun to conduct unannounced inspections in India, with plans to expand to China, where FDA already has field offices and inspection staff.[37] FDA stated the unannounced inspection program was launched in India first since foreign inspections in certain parts of China are still paused due to local COVID-19 restrictions.[38] Regarding other parts of the world, in January 2022, the Creating Efficiency in Foreign Facility Inspections Act, S. 3509 was introduced in the United States Senate, proposing to expand FDA's ability to perform unannounced inspections of foreign facilities. While this would strengthen FDA's mandate, logistical challenges for FDA investigators such as arranging travel and securing visas would remain.

Now that the COVID-19 pandemic has begun to subside in 2022 and public health measures such as travel restrictions are largely lifted, FDA has resumed onsite inspections. However, the agency continues to use the inspectional techniques it piloted during the pandemic and rely on updated quality data metrics to focus its resources on inspections of highest risk to the public health.[39] The new approach offers significant advantages which FDA can benefit from beyond the pandemic for all types of FDA-regulated products. FDA has stated that its revised approach will enhance oversight and "improve […] the efficiency of how [they] operate, furthering [their] mission to protect the public health." The adoption of these inspection techniques also reflects FDA's "modernization effects" in implementing "advanced tools, including technology."[40]

Conclusion

In light of FDA's updated inspectional approach, pharmaceutical manufacturers should also update and revise their standard operating procedures on inspection management. With increased visibility to manufacturers through remote review and information sharing, it is highly likely that an FDA investigator's first impression of a facility will occur before their arrival. This also means that documents such as manufacturing and data integrity-related investigations and reports, which are typically viewed onsite, are now particularly susceptible to advance review. Regulators may use these documents to prepare for an upcoming inspection or base regulatory decisions solely on them. Manufacturers should, as a result, consider creating or updating policies related to FDA record requests and remote interactive evaluation requests. Companies should prepare in advance for the disclosure of challenging manufacturing deviations discovered over the past few years and be in position to explain the corrective and preventive measures taken to demonstrate sustainable cGMP compliance. Finally, practicing how to handle, manage, and respond to an unannounced inspection helps, and companies should conduct regular "mock audits" and document reviews to stay in a state of

inspection readiness, including identifying the best subject matter experts for potential interactions with an investigator.

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FACILITY TOUR

Eurofins BioPharma Product Testing

ATMP and Cell and Gene Therapy Testing Services for the Global Market

The global biopharmaceutical industry is continually innovating and looking forward to discover the next class of therapies to treat and cure patients around the world.

Cell and gene therapies, which fall into the broader category of drugs known as Advanced Therapy Medicinal Products (ATMPs) have emerged as an incredibly promising class of treatments that have shown the ability to treat and even cure many individuals with diseases for which there was previously little to no hope.

Cell and gene therapies work by substituting the missing or defective gene and resulting protein or cell causing the disease's symptoms. Cell therapy treats diseases by restoring or altering targeted sets of cells or by using cells to carry a therapy throughout the body. Gene therapy operates differently by replacing, inactivating or introducing genes into cells — either inside the body (*in vivo*) or outside of the body (*ex vivo*). Some therapies are considered both cell and gene therapies. These therapies work by modifying genes in specific types of cells and inserting them into the body.

Current market forecasts predict the cell and gene therapy market to grow by almost $10B by 2026. A compound annual growth rate of more than 20%.[1]

Clearly the cell and gene therapy market indicates immense growth potential. But, with this massive increase, comes the need for the research, development, testing, and manufacturing services to bring these products to patients quickly, efficiently, and with this highest possible quality and safety.

Eurofins BioPharma Product Testing (Eurofins BPT) supports the development of ATMPs both for traditional use as well as for use in personalized medicine. The company provides comprehensive cGMP-

compliant CMC testing support to ensure the identity, potency, purity, and safety of starting materials, intermediate products, vectors, and final drug products as well as support for manufacturing process development and validation.

Responding to a Growing Market

Eurofins BPT is experiencing significant growth in cGMP testing of both traditional biologics (mAb/protein therapeutics) as well as Cell & Gene Therapy (CGT) products or ATMPs. To address the growing demand for testing across biologics and the challenges posed by the growing ATMP sector, Eurofins BPT is increasing the size of many of its laboratories and adding a new lab focused specifically on viral vectors and ATMP product testing. This is all part of an overall strategy to support the ATMP product testing demands as well as expansion of the viral safety, biochemistry, and molecular testing services that the company's ATMP clients require.

Commenting on this growth, Marian McKee, PhD, Vice President of Biosafety said, "The ATMP lab was designed to accommodate many of the tests required to release viral vectors for use in cell and gene therapy applications. The space includes cell-based assay capabilities with various endpoints, including a PCR suite and immunoassay set up to accommodate endpoint analysis. The first methods to be launched out of the CGT/ATMP lab will be the replication competent and viral vector quantitation assays. The space is also designed to accommodate basic biochemistry set up for release testing and affords space for future expansion as demand grows."

A Closer Look at ATMPs and Cell and Gene Therapy Services

"Eurofins BPT has a long history of offering cGMP-compliant CMC testing of starting materials, intermediate products, vectors, and final drug products and supporting manufacturing process development and validation," says Marian McKee. "This includes testing of raw materials, cell and viral bank services, plasmid and viral vector testing, lot release testing, bulk and finished product testing, and stability studies."

For cell and gene therapy products, Eurofins BPT provides cGMP testing services to support both autologous and allogeneic cell therapies, including rapid sterility (BAcT/Alert 3D technology) and mycoplasma (MycoSEQ Real Time Detection System for Mycoplasma). Within the Eurofins BPT network of companies, analytical ultracentrifugation to support regulatory expectations around empty/full capsid analysis has been added recently. Eurofins BPT has also invested in technology to allow rapid sterility testing requirements for autologous cell therapies and digital droplet PCR for more precise quantitation of viral particles. Investments in Eurofins BPT facilities expand CGT capabilities and include laboratories being updated to accommodate biosafety level 2 (BSL2) work to maximize space utilization and to optimize workflows.

Investments in Cell and Gene Therapy Testing Technologies

With the industry's drive to bring more cell and gene therapy products to patients, comes the inevitable need to implement the latest technologies and instruments to test and analyze these ATMPs. Eurofins BPT is making significant investments in facilities and instruments to ensure the company has the most up-to-date capabilities.

"As clients' needs and market trends evolve, we've been in lockstep by expanding our lab space and capabilities specifically with our new transmission electron microscopy (TEM) lab in a newly built laboratory space designed to support the company's ATMP testing offering," said Marian McKee.

The addition of electron microscopy allows Eurofins BPT to offer a full panel of *in vitro* test methods required for bulk harvest (UPB) testing and cell line characterization (CLC). The TEM lab will complement the cell and gene therapy testing services for viral vector characterization, including analysis of capsid architecture and empty/full analysis.

Marian McKee continues, "In addition to the new lab space for TEM, Eurofins BPT is investing in expansion of molecular biology, biochemistry, sterility, mycoplasma, viral safety, and raw materials testing, as well as stability laboratories across its Lancaster campus. Much of these enhancements are in response to the growing demand from the advanced therapy market."

The addition of new instrumentation and technology is designed to handle the smaller sample volumes inherent to cell and gene therapy and for specialized testing. Examples include ddPCR, Maurice, Ella, Flow Cytometers and Analytical Ultracentrifugation (AUC).

Global Support for ATMP Capabilities

Eurofins BPT has the largest network of harmonized bio/pharmaceutical cGMP product testing labs around the world in order to provide services to the global biopharmaceutical industry.

As the need for ATMP services in general and cell and gene therapies specifically grows, Eurofins BPT is investing in facilities, technologies and personnel worldwide to meet the burgeoning demand.

"In the the United States, the Lancaster, PA, laboratory is the lead site in development of advanced capabilities and offers transfer of methods to support clients working with Eurofins BPT sites in Columbia, MO, and San Diego, CA," says Marian McKee.

As the modalities employed for gene therapy change, Eurofins BPT is able to adapt existing capabilities or add new ones to address the emerging market. Currently, Eurofins BPT is able to support testing and release of:

- Viral vectors for *in vivo* and *ex vivo* use
- Nanoparticles
- Plasmid based
- iRNA/mRNA
- Oncolytic Viral Therapies
- Allogeneic and Autologous Cell Therapies

In addition, Eurofins BPT has built global teams that are focused on various product modalities, including traditional biologics and cell/gene therapy.

"The global teams are tasked with sharing information about regulatory trends, new testing approaches, and market demands from both local and international geographies," says Stanley Prince, Senior Scientific Advisor Manager.

The company's laboratories in Europe and Asia Pacific are also making significant investments to support the cell and gene therapy cGMP testing requirements. Some of the investments include ddPCR, NexGen Sequencing, Viral Safety, and many more.

For product specific methods such as potency, infectious titer, and others, Eurofins BPT has the ability to transfer methods for cGMP testing between sites to accommodate product release in the various geographies under various regulatory umbrellas.

The Future of ATMP and Cell and Gene Therapy Testing Services

As the global market for these therapies continues to expand, Eurofins BPT is committed to bringing the latest tools and technologies into use for its current and future clients.

"We are continuing to gather information from our clients directly as well as from conferences," says Stanley Prince. "The information we gather helps us to evaluate investments into new technologies and methodologies to support the cGMP testing requirements of these therapeutics."

In addition, Eurofins BPT also participates in various regulatory strategy review committees to review new guidance documents and provide feedback to the agencies, discusses traditional biologics testing problems that may negatively impact the cell and gene therapy industry, and works collaboratively with companies globally to bring new alternative approaches to help further progress the development of these much-needed therapeutics.

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Ross Blezard
Product Application Specialist in DFE Pharma's Biopharma division

The administration route of a drug is a critical decision during medicine development: it can decide the success or failure of the drug product. During the development process clinical factors (such as efficacy in humans and patient compliance) as well as commercial factors (such as development and manufacturing costs) have to be taken into account. There are many defined routes of administration, which can be loosely classified into three groups: Enteral, where a medicine is delivered through the gastrointestinal tract, for example with tablets and capsules. Parenteral, which in strict terms would indicate any route other than the enteral route, however, is commonly associated with injectable routes such as intravenous (IV), intramuscular (IM), intradermal (ID) or subcutaneous (SC). Whilst parenteral administration routes are effective from a clinical standpoint, they are not considered patient-friendly administration routes (specifically IV). The final administration route we can term as "other"; this is where inhalation and pulmonary delivery may offer a patient-friendly alternative to IV.

Pulmonary delivery of a water-soluble API has a multitude of benefits over other established patient-friendly routes of administration, like oral delivery. The large surface area available for absorption in the lungs typically results in a rapid and predictable onset of action. Pulmonary delivery largely avoids the first pass metabolism, meaning that higher concentrations of the active drug are available at the site of action. Additionally, drug delivery to the targeted tissue area can result in fewer side effects.

Pulmonary administration is currently an essential route in the treatment of respiratory conditions. Dry powder inhalers (DPIs), are non-invasive devices designed to deliver dry powder to the lungs upon inhalation. DPIs have been used in the treatment of diseases, such as asthma and chronic obstructive pulmonary disease (COPD), for decades. Pulmonary drug delivery is a growing area with new products designed to treat everything from diabetes to neurological conditions currently making their way through the development pipeline and into clinical practice.

DPIs have advantages over other forms of pulmonary administration devices like nebulizers, metered dose inhalers and soft mist inhalers (see Table 1). They are, for example, portable, easy to use, and contain the formulation in a dry form. What's more, they have a relatively low

Table 1. The advantages and disadvantages of common pulmonary delivery systems[1]

Delivery system	Advantages	Disadvantages
Dry powder inhaler (DPI)	• Requires lower levels of patient coordination than other methods • Compact/portable • Quick and easy to use	• Drug preparation differs between DPI devices • Higher inspiratory flow required
Pressurized metered-dose inhaler (pMDI)	• Compact/portable • Quick and easy to use	• Requires high levels of hand-mouth coordination • Propellant required
Nebulizer	• Can be used with different drugs/doses • No hand-mouth coordination required	• Bulky / not portable • Requires a power source • Takes longer to deliver treatment • Drug wastage levels necessitate higher doses
Soft mist inhaler (SMI)	• Compact/ portable • Low drug flow • High fine particle fraction	• Requires higher level of coordination • Small quantities per dose • Drug needs to be soluble

carbon footprint because, unlike pressurized metered-dose inhalers (pMDI), they do not contain a propellant.

Trends in the Industry

In order to expand and fully utilize the inhaled route there is a requirement to deliver high drug doses (for example in the case of antibiotics). Additionally, with the increasing popularity of biologics and complexity of dose adjustment, pulmonary delivery can be an ideal platform to accommodate the formulation of this class of complex molecules.

Delivering High Doses

The efficacy of an inhaled drug heavily relies on the deposition of the active pharmaceutical ingredient (API) into the lungs, and it is the aerodynamic particle size distribution (APSD) that defines how powders behave in an airstream during inhalation.

Generally, API particles after crystallization require size reduction to allow inhalation delivery. The optimal aerodynamic particle size to reach the bronchial region is <5 µm, with the majority of the particles being 2-3 µm.[2] Traditionally, top-down processes, like micronization, are used for the particle size reduction. This approach presents flowability and dispersibility challenges. Particles with lower particle size have high surface area and hence high adhesive forces. Overcoming these challenges relies on the careful design of both the powder blend and the DPI device.

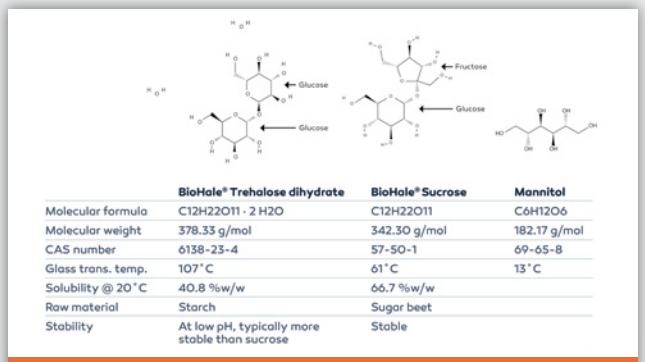
The most common approach to address these challenges is to formulate APIs with a carrier excipient, usually lactose monohydrate. The carrier has coarser particles than the API, typically between 50 to 100 µm in diameter, and form a loose bond with the drug.[2] As the formulation is inhaled, the drug detaches from the carrier particle, allowing the drug to be delivered to lungs and the carrier to be deposited in the throat and swallowed. Using a carrier also aids fluidization and dispersion, improving the flow of the formulation to aid processing steps such as device filling and dose metering.

This approach is referred to as "carrier-based" formulation and is well established for the majority of formulations and it works very well. Both the powder blend and the DPI device must be carefully designed to ensure detachment of the micronized drug from the carrier excipient on inhalation.

DPIs are typically designed to deliver API doses of microgram quantities. For example, the Ellipta® product range contains 40 µg of vilanterol trifenatate and 74.2 µg umeclidinium bromide with a total powder mass of 12.5 mg (mainly lactose monohydrate).[3] For some APIs however, higher doses are required to achieve the desired therapeutic effect. As drug loading increases, it becomes increasingly challenging to maintain the correct adhesion-cohesion balance, whilst avoiding powder blend challenges such as uniformity and segregation. In the traditional carrier-based model, an increased delivered dose therefore requires a corresponding increase in excipient, which may come with some challenges. Large volumes of powder threaten effective drug-carrier separation, and can be difficult to inhale, threatening dose uniformity. Large powder volumes are also associated with side effects, the most commonly reported being coughing. Aside from being unpleasant, in people with pulmonary diseases, such a lung cancer or Cystic Fibrosis (CF), coughing can irritate and damage the lung, adding to the likelihood of adverse outcomes. In addition, introducing large volumes of powder to the lungs increases the chances of the drug being removed via mucociliary clearance.[4]

The Rise of Biologics

Biologics are a class of medications that offer unique treatment options for many of the world's most challenging diseases. The terms



	BioHale® Trehalose dihydrate	BioHale® Sucrose	Mannitol
Molecular formula	C12H22O11 · 2 H2O	C12H22O11	C6H12O6
Molecular weight	378.33 g/mol	342.30 g/mol	182.17 g/mol
CAS number	6138-23-4	57-50-1	69-65-8
Glass trans. temp.	107°C	61°C	13°C
Solubility @ 20°C	40.8 %w/w	66.7 %w/w	
Raw material	Starch	Sugar beet	
Stability	At low pH, typically more stable than sucrose	Stable	

Figure 1. Key properties of some high purity, low endotoxin grade stabilizers that are typically used in particle engineered DPI formulations.

biologics and biopharmaceuticals cover a broad class of molecules that include, among others, peptides, proteins, nucleic acids as well as blood, tissue, cell and gene products. Biologics have the potential to change patient lives significantly. For example, in some types of cancer, biologics constitute the first new treatments in decades. In fact, biologics appear to show promise across almost all disease areas as well as many diagnostic applications. The expectation is that biologics will significantly overtake innovative small molecules sales over the next five years. By 2027, biologics sales are forecasted to exceed small molecules sales by $120 billion.[5]

Biologics are a complex class of drug. They typically have a poor stability profile (compared to small molecules), and are often sensitive to temperature, light and pH changes. Additionally, they have poor permeability through the intestinal epithelium and are susceptible to enzymatic degradation in the gastrointestinal tract.[6] This means that, historically, biologics have been administered parenterally, despite this being invasive and inconvenient for the patient, and resource hungry for healthcare systems.[7]

In recent years, inhaled formulations and DPI systems have become widely accepted as an alternative to the SC and enteral (oral) administration of therapeutic peptides and proteins. They avoid the potential of poor absorption and high metabolism in the gastrointestinal tract, and the first-pass effects in the liver. In addition, inhalation therapy, unlike injection delivery, is pain free making it more convenient for patients. Whilst this is a highly active area of research in general terms, for smaller biologics, such as insulin, systemic delivery is possible and for larger molecules, such as monoclonal antibodies (mAbs), local treatment of the lung tissue is possible.

Traditional 'carrier-based' DPI drug delivery, however, is not always suited to the delivery of these promising molecules, particularly those that require additional stabilization. Stresses from size reduction, but also during storage and handling, can reduce the activity of biologics. Alternative processing strategies are required, and the use of excipients to stabilize the biologic and improve powder properties may be required.

Excipients in Spray Drying

Particle engineering offers an alternative route, which is especially suitable for high dose and biological formulations. Spray drying is the most commonly used technology for particle engineering in DPI, although also other alternatives exist, like spheroid formation or freeze drying. Spray drying can be used to modify the particle morphology of the API, resulting in a reduced aerodynamic diameter without having poor flow and poor aerosolization properties. The physical properties of spray-dried particles are highly dependent on the process parameters used and the composition of the spraying matrix. Without excipients, material properties are highly dependent on the properties of the drug. Unfortunately, very few molecules can be directly spray-dried with the desired physical properties without the addition of excipients. Excipients are added to improve the general powder handling, or they can be added to protect the API from external stresses.

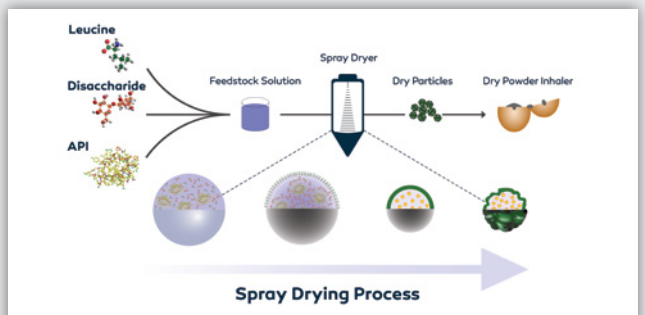


Figure 2. Visual representation of a spray drying process of a biologic with a disaccharide and leucine. Disaccharide molecules shield the biologic to protect them against external stresses, and leucine typically accumulates at the surface.

Whilst many excipients are described for this application in literature, three excipients in particular show great promise for use as a filler in the spray-drying processes. These are trehalose and sucrose, which are non-reducing crystalline disaccharides, and the sugar alcohol mannitol. All three provide improved compatibility with biomolecules compared to reducing sugars. They are not easily hydrolyzed by acid, and they can help these complex molecules maintain their native conformation. In addition, they can enable modification of the resulting powder's physical properties. They also have an excellent safety profile and are commonly used as lyo- and cryo- protectants in parenteral administration of therapeutic proteins.

Trehalose and sucrose are particularly attractive due to their high glass transition temperature. This enables the formation of a glassy amorphous matrix, which in turn may be particularly suited to maintaining the stability and activity of biomolecules. In addition, when compared to other disaccharides, trehalose is highly stable under low-pH conditions.

Because trehalose can function as a particle matrix/stabilizing agent, it is a promising excipient for the delivery of biomolecules, such as peptides and proteins. Sucrose could also play a role in this area, and it has a demonstrated utility as an excipient for peptide and protein delivery, for example it is already being utilized in many biologic formulations, including COVID vaccines.

Mannitol has a much lower glass transition temperature, when compared to sucrose and trehalose, typically reported to be approximately 13℃. The impact of this is that it tends to crystalize after spray drying. The transition from an amorphous material to crystalline material may introduce stresses that can damage sensitive molecules, such as biologics. However, many molecules can tolerate these stresses, and in some cases, it may be preferable to have the more thermodynamically stable crystalline form. If an amorphous glass is required, then the crystallization of a matrix containing mannitol can be impeded with the addition of further excipients such as glycine and inorganic salts. Additionally, mannitol has a proven application in pulmonary delivery due to its use in Exubera®, the first inhaled insulin dry powder inhaler that was available in the market between 2006 and 2008.[8]

It should be noted that the three mentioned excipients would typically not be used in isolation; amino acids, and specifically leucine types, are commonly utilized in academic research to enhance the aerosolization properties of spray dried particles for pulmonary drug delivery. During the spray drying process, leucine molecules accumulate at the surface of droplets with their hydrophobic part facing the gas phase. When the concentration of leucine increases at the surface and supersaturation is achieved, leucine crystallizes at the outer surface, forming a shell. This benefits the aerosolization performance, as it results in lower cohesion forces within the particles. Figure 2 shows a graphical representation of the spray drying process of a biologic with a disaccharide and leucine. Disaccharide molecules shield the biologic, while leucine accumulates at the surface and has more impact on the physical surface properties of the spray dried powder.

Embracing the Potential of Next-Generation Inhaled Medications

Drug developers are expanding the use of inhaled medications in a bid to tackle unmet medical needs. However, with high-dose medications and biologics being unsuited to the carrier-based DPI model, this new dawn requires new formulation processing techniques.

Spray drying is emerging as one of the most promising carrier-free technologies and has already yielded important results. Careful consideration of excipient use within this emerging area of interest can help developers create bespoke formulations that meet the characteristics of the API and the needs of the patient alike.

As discussed in this article, the field of pulmonary delivery is expanding from small molecule delivery to biologics and from low dose to high dose formulations. The authors believe that this is just the start in targeting the delivery of new and existing medicine to the lungs. This shift is occurring now, for example, inhaled cannabinoids can deliver higher efficacy at lower doses than orally delivered products. This approach has shown some promise in therapy areas, such as cancer treatment-associated nausea, depression, anxiety, migraine, and pain, among others.[9] Researchers in lung cancer,[10] pulmonary hypertension,[11] and Alzheimer's disease[12] are also investigating the benefits of pulmonary delivery. All in all, it's an exciting and promising moment in this field.

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Author Biographies

Pauline van der Wijst-Janssen *is a Product Application Specialist at DFE Pharma. She has been working on application development of excipients based upon fundamental knowledge of excipients and powder physics. She joined DFE Pharma in 2017 and worked as a product developer and application specialist on multiple OSD and DPI projects. Pauline holds a Master's Degree (cum laude) in Physical Chemistry from the Radboud University in Nijmegen, with an additional specialization in Science, Management and Innovation. Since April 2022, she is also affiliated with the University of Groningen with a PhD student position.*

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Endotoxin Testing Considerations – Reducing LAL Use with Compendial Methods

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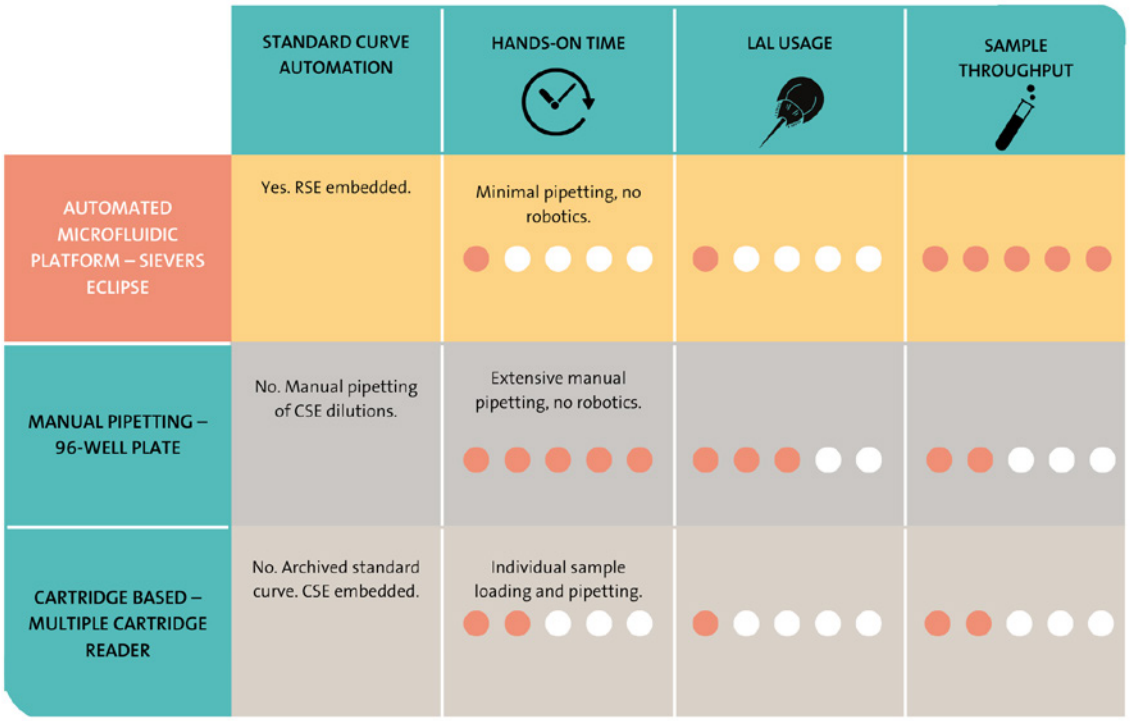
***Hayden Skalski** is the Life Sciences Product Application Specialist for the Sievers Instruments product line, specializing in bacterial endotoxins testing (BET). Hayden has over 8 years of experience in the pharmaceutical industry and Quality Control Microbiology and has presented on numerous topics surrounding endotoxin testing. Previously, Hayden held roles at Charles River Laboratories, Regeneron and Novartis, validating and executing method development protocols for endotoxin testing, providing customer support, troubleshooting and supporting high-volume product testing. Hayden has a B.S. from the University at Albany (SUNY) in Biology.*

The link between horseshoe crabs and pharmaceutical and medical device manufacturing is an important subject today in the biomedical industry - an industry that is prioritizing sustainability while also ensuring safety and quality of products for patients. The blood from horseshoe crabs contains factors that are used to manufacture limulus amebocyte lysate (LAL), a reagent that can test whether drug products or medical devices have been contaminated with bacterial endotoxin. Through a series of cascade reactions, the crab's blood factors have a clotting mechanism in place to detect any introduction of bacterial harm. This testing is critical to detect dangerous – and potentially deadly contaminants – but it puts pressure on horseshoe crabs and their desired blood.

The Atlantic horseshoe crab, *Limulus polyphemus*, is a species of marine arthropod found along the eastern coast of North and Central America. The Delaware Bay supports the largest spawning population in the world.[1] The limulus species is around 450 million years old and is one of the most studied invertebrates in the world due to its unique blood. Horseshoe crabs are widely used for a few purposes such as a food source for birds (eggs), bait for commercial eel and conch fisheries, and the biomedical industry.[1] Baiting of horseshoe crabs, particularly in the Northeast region, is allowed and is seen as the main cause of mortality and declining population of the Atlantic horseshoe crab species. Atlantic coastwide bait landings in 2020 were reported at 456,675 crabs.[1] In the Southeast Atlantic state of South Carolina, harvesting of horseshoe crabs for any bait use is prohibited through law.[2] All fisheries who capture and collect horseshoe crabs must possess a proper permit for commercial, educational, or private purposes.[2] This law is extremely important to the horseshoe crab population, as it allows the population to flourish in the southeast and protects the crab species from baiting. As mentioned previously, a large population of the Atlantic horseshoe crabs is collected for the biomedical industry to support production of LAL reagent. Blood from the horseshoe crab is obtained by collecting adults and extracting a portion of their blood. Most crabs collected and bled by the biomedical industry are, as required by the Fishery Management Plant (FMP), released alive to the water from where they were collected; however, a portion of these crabs die from the procedure.[1] Per the state compliance reports in 2021, the population of crabs have a very low mortality rate from biomedical use compared to the main source of mortality which is baiting. The 2019 Horseshoe Crab Benchmark Stock Assessment evaluated the stock status of the resource by region, finding populations within the Delaware Bay and Southeast regions remaining consistently neutral and good, respectively, through time.[1]

Due to the concerns of crab populations and the dependence on their blood for biomedical purposes, the awareness of alternative bacterial endotoxin methods has risen as of recent years. Recombinant Factor C (rFC) and recombinant LAL (rLAL) are two alternative methods which do not use horseshoe crab blood. rFC is the first clotting enzyme in the horseshoe crab's blood clotting mechanism, and a clone of this Factor C is used for the rFC method. This alternative



	STANDARD CURVE AUTOMATION	HANDS-ON TIME	LAL USAGE	SAMPLE THROUGHPUT
AUTOMATED MICROFLUIDIC PLATFORM – SIEVERS ECLIPSE	Yes. RSE embedded.	Minimal pipetting, no robotics.		
MANUAL PIPETTING – 96-WELL PLATE	No. Manual pipetting of CSE dilutions.	Extensive manual pipetting, no robotics.		
CARTRIDGE BASED – MULTIPLE CARTRIDGE READER	No. Archived standard curve. CSE embedded.	Individual sample loading and pipetting.		

Based on average 8-hour shift using a single platform.

method is an end-point method, meaning one reading is taken at the beginning of the test, and then one at the very end. It works by a fluorescence reader amplifying a fluorogenic substrate when endotoxin is detected. Since this is an alternative method for detection of bacterial endotoxin, a company must go through additional and rigorous testing to show equivalency to the compendial BET methods. The FDA has recognized rFC as an alternative method, and states firms may use alternative methods and/or procedures if they provide advantages in terms of accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction, and in other special circumstances.[3] If a company chooses to use the rFC assay, then alternative method validation should be performed in accordance with the requirements of USP <85> Bacterial Endotoxins Test and USP Chapter <1225> Validation of Compendial Procedures.[3]

Recombinant LAL reagent, or rLAL, is also an alternative test. It utilizes the same cascade as traditional LAL reagents. This means it contains all the factors that are responsible for detecting endotoxin that are found in horseshoe crab blood using a recombinant manufacturing process.[4] This a step forward in the process of using a recombinant reagent as it contains all clotting factors and uses a traditional kinetic assay on an absorbance reader. Although it is a step forward in animal-free testing for BET, it is still considered an alternative method and companies must go through the same time consuming and rigorous process as rFC if they choose to use this assay. Since trying to validate and implement an alternative method for BET is not easy, some firms may ask what other solutions are currently available to help achieve a more sustainable and efficient way to test products for endotoxin.

The Sievers Eclipse Bacterial Endotoxins Testing (BET) Platform is one solution that offers significant advantages in terms of LAL reduction and compliance. The Eclipse reduces LAL use by up to 90 percent while remaining compliant with all global pharmaceutical regulations. This is a substantial improvement compared to traditional LAL methods such as the 96-well plate and gel clot. For the Sievers Eclipse BET platform, a novel microplate was designed that facilitates accurate and rapid dispersion of LAL and samples using centripetal force, metering chambers, and microfluidic channels. The microfluidic system enables users to carry out the same biochemistry that is performed in traditional endotoxin assays but with minimal hands-on effort, greater consistency, and drastically reduced LAL consumption. By decreasing horseshoe crab lysate use by up to 90%, the Eclipse platform reduces the demand on the most sensitive and unmatched natural endotoxin detection reagent on the planet. The Eclipse platform uses commercially available, FDA licensed LAL and meets all requirements of the harmonized global pharmacopoeia, USP <85>, EP 2.6.14 and JP 4.01. This empowers users to be conscious of today's needs to protect valuable natural resources while still complying with the strict analytical and regulatory requirements drug and device manufacturers must meet.

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Detecting Trace Elements in Single Cells with ICP-MS

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Trace elements are crucial to many biological processes. From the wound-healing effects of zinc to the enzymatic control of iron and copper, and the potential anti-cancer benefits of selenium, trace elements are critical to physiological and biochemical processes in plants and animals.

To fully understand trace element uptake and processing, intracellular levels of trace elements must be determined. By detecting both the distribution and mass concentration of trace elements within cell populations, scientists can gain greater insight into cellular function and heterogeneity within populations. This knowledge can help:

- Improve understanding in clinical research, through the detection of metal toxins.
- Drive better drug efficacy, by detecting metallodrug uptake.
- Define optimal cell culture conditions for bio-production research, by analyzing consistency markers within cultures.

Although biomarker analysis is routinely used in clinical research, diagnosis and treatment, trace metal analysis has lagged. This is largely because traditional methods, which rely on cell digestion, assume homogeneous distribution of analytes through the cell cohort. This is not the case with trace elements and these methods do not give the detail needed to discern the nuances of intracellular distribution.

However, recent advances in inductively coupled plasma-mass spectrometry (ICP-MS) are changing this landscape. These powerful, element-selective detection systems now provide the capacity and capability for trace element analysis at the single-cell level. This paper shows how scientists can use the latest ICP-MS technology and software to accurately determine the amount of trace selenium in individual cells using certified reference samples of selenized yeast.

What is Single-Cell Analysis and Why is it Important?

As the title suggests, single-cell analysis is the determination of trace elements in individual cells. Understanding trace element presence and concentration at the cellular level is imperative as there is often great heterogeneity, even within the same cellular population and in ideal conditions. Without understanding the spectrum of a trace element's presence and its mass within individual cells, the nuances of its impact on a cell, a population or even a bioculture cannot be fully elucidated.

Traditional trace-element analysis methods involve digesting large numbers of cells and analyzing the metal content within. Although effective at measuring total trace element mass, these methods do not account for cell-to-cell variation and cannot identify the number of cells containing the element or the concentration contained within. This means that valuable insights contained within the cells are lost.

Effective single-cell analysis is needed to accurately quantify the average mass per cell and identify the element distribution across cell cohorts (number concentration). These measurements are established through two main calculations (Figure 1).

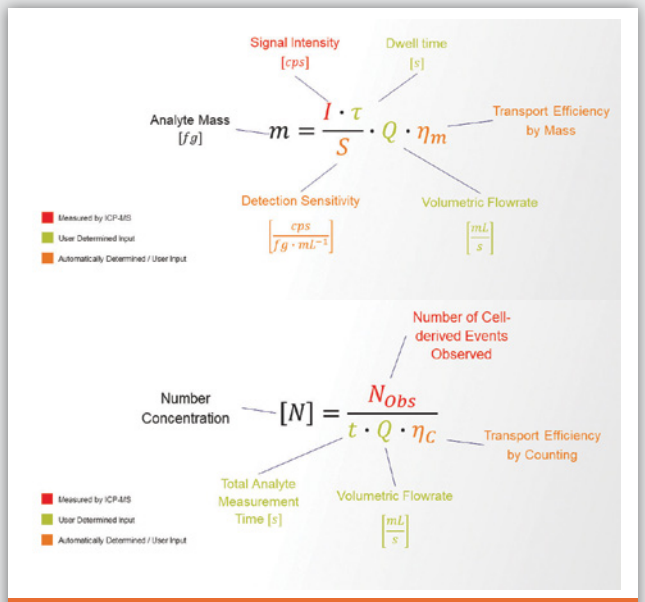


Figure 1. Calculations for analyte mass and number concentration used in single-cell trace element analysis.

Due to recent advances in ICP-MS technology, two key factors in these calculations can now be observed: signal intensity and the number of cell-derived events (shown in red), but the technology and its software also bring other important accuracy benefits. By using optimized workflows and tailored equipment that helps to protect the cells, transport efficiency and detection sensitivity can be improved. Transport efficiencies (for transferring cells from the sample to the plasma source of the ICP-MS) of greater than 70% can now be routinely achieved and high detection sensitivity, (measured through a standardization curve and accounting for element ionization, focusing and detection within the ICP-MS instrument), is achievable for a wide range of elements.

The latest software can also help increase efficiency, improve throughput and lower laboratory costs by automating the user-determined inputs (shown in green). Algorithms built into the software can accurately measure transport and detection efficiencies and use analytical parameters to suggest optimized volumetric flow rates and dwell times to improve these rates.

scICP-MS: Reaching New Levels of Sensitivity and Speed for Single-Cell Analysis

So-called single-cell ICP-MS (scICP-MS) is a technique that utilizes the single-cell mode of the latest ICP-MS technology and can analyze multiple trace elements (in sequential order) from a single sample.

The sample is nebulized to form a stream of single cells for individual analysis. The resulting cells are then ionized, and ion optics focus the beam into a quadrupole mass analyzer where ions, separated according to their mass-charge ratio (m/z), are detected.

The latest scICP-MS technology provides very low detection limits in low sample volumes, increasing sensitivity and allowing even low levels of trace elements to be accurately identified. Added to this, simple sample preparation methods and high throughput workflows mean that a greater number of samples can be analyzed, even at the single-cell level. Part of this efficiency comes from the technology's ability to control interference and reduce background noise, meaning that analysis of complex cultures requires minimal preparation steps.

However, to achieve high levels of efficiency and throughput while maintaining accuracy, scICP-MS technology must be used in combination with complementary technology and software.

Firstly, specialized nebulizers must be used to decrease the flow rate. This protects the cells from damage and ensures a stream of single cells for individual analysis with high transport efficiency.

Secondly, specialized software helps to drive key elements of the workflow to maximize detection accuracy and efficiency. Decreased dwell times enable detection of the very short, transient signals that are emitted from single cells and sequential analysis programs help to reduce settling times, maximize duty cycles to fully measure m/z, and split sample time equally among analytes (if multi-analyte measurement is needed).

Finally, data packages can automate evaluation parameters for more accurate calculations. Known cell suspension standards can be used to calculate transport efficiency and detection sensitivity can be calculated by calibrating against ionic standards. Once the data is

collected, raw data and signal-distribution views can be displayed to accurately identify fractions, modify thresholds and interrogate mass-distribution information. In turn, mean and median analyte mass and number concentration figures can be calculated from this data representation.

Measuring Selenium in Selenized Yeast with scICP-MS

Selenium (Se) is a trace element micronutrient and antioxidant that is thought to protect individuals from thyroid disease, cancer, cardiovascular disease and even cognitive decline.[1] Recent research delivering Se via selenized yeast has shown reduced low-density lipoprotein profiles in patients with atherosclerosis[2] and reduced recurrence of tumors in patients who initially had an advanced adenoma.[3]

The bioavailability and low cost of selenized yeast make this a promising supplement and potential treatment for some diseases. However, Se can be present in many different forms in yeast – organic as selenomethionine,[4] inorganic as selenite or selenate,[5] and also in nanoparticle form.[6] To understand the full potential of how selenized yeast might be used in disease prevention and treatment, plus how reliable bioproduction can be maintained, full analyses of the mass and distribution of Se in yeast are crucial.

In a recent experiment, the Thermo Scientific™ iCAP™ TQ ICP-MS triple quadrupole system in single-cell acquisition mode was used to evaluate the presence of Se in a certified reference material sample of lyophilized yeast cells (SELM-1), a type of selenized yeast. Phosphorus (P) was also evaluated as a cell marker, since it is a constituent element in yeast cells, e.g., as a part of the DNA backbone. In this study, the most common isotopes of both elements were measured in their ionic forms: $^{31}P+$ and $^{80}Se+$.[7]

By comparing P and Se events as detected through the ICP-MS instrument, the fraction of Se-containing cells could be calculated, as well as the mean and median mass of the analytes within the cell population.

Method

SELM-1 cells were resuspended in water, washed twice by centrifugation and then diluted to a final concentration of 50,000 cells per mL, as confirmed by flow cytometry. Specialized nebulizers and spray chambers were then used to deliver a single stream of cells to the scICP-MS while protecting their delicate structure. High transport efficiencies of greater than 70% were achieved and confirmed by the linked software.

The iCAP TQ ICP-MS was used in TQ-O_2 mode to induce oxidation and reduce polyatomic interferences. P and S were measured via the product ions $^{31}P^+$ $^{16}O^+$ and $^{80}Se^+$ $^{16}O^+$. The exact parameters established for the separation and detection stages are shown in Table 1.

Table 1. Instrument parameters set for the study of SELM-1 cells

Parameter	Value
Nebulizer	MicroMist™ HE U-Series nebulizer
Spray chamber	Total consumption spray chamber
Sample delivery	Chemyx™ Fusion 100-X syringe pump
Sample flow	10 µL/min
Forward power	1,550 W
Nebulizer gas flow	0.51 L-min^{-1}
Sheath gas flow	0.65 L-min^{-1}
Interface configuration	High sensitivity
Analysis time	60 s per element, 250 s total duration (including uptake and wash)
CCT settings	
CRC gas flow	0.35 mL-min^{-1}, 100% 0_2

The scQuant plug-in for Thermo Scientific™ Qtegra™ Intelligent Scientific Data Solution™ Software was used to create the method and provide data evaluation post-analysis. Data were acquired using the time-resolved analysis mode at a dwell time of 5 ms and a detection sensitivity of 0.2 µgL^{-1} was achieved for Se, equivalent to a minimum detectable amount of 0.17 Se fg per cell.

Results

Quantitative assessment of the resulting ICP-MS signals allows the determination of three key metrics: the number of cells that contain a quantifiable amount of each element, the average mass of each element within a cell and the distribution of each element across the cell cohort.

The raw data indicates that the number of detected signals per unit of time was slightly lower for Se than for P. This demonstrates that, although each cell contains a significant amount of P (known to be present in DNA), not all cells contain Se and, therefore, only a fraction of the total cells showed detectable levels of Se (Figure 2). In fact, 57% of cells had detectable levels of Se, in the range of 2.5 fg – 72.5 fg.

Further analysis showed a broad distribution of Se in the cell population, a mean of 18.6 fg and a median of 16.8 fg were detected with a standard deviation (SD) of ± 12.5 fg. The mean for P was 37.0 fg and the median 30.9 fg, across the cell population, with an SD ± 23.1 fg (Figure 3). Although the SD was lower for the Se data, it was based only on the detected cells and the overall score would have shown greater inhomogeneity.

scICP-MS is an Effective Tool for Analyzing Trace Elements in Single Cells

This study into the presence of Se and P in selenized yeast demonstrates that scICP-MS, used in single-cell mode, is an effective tool for the

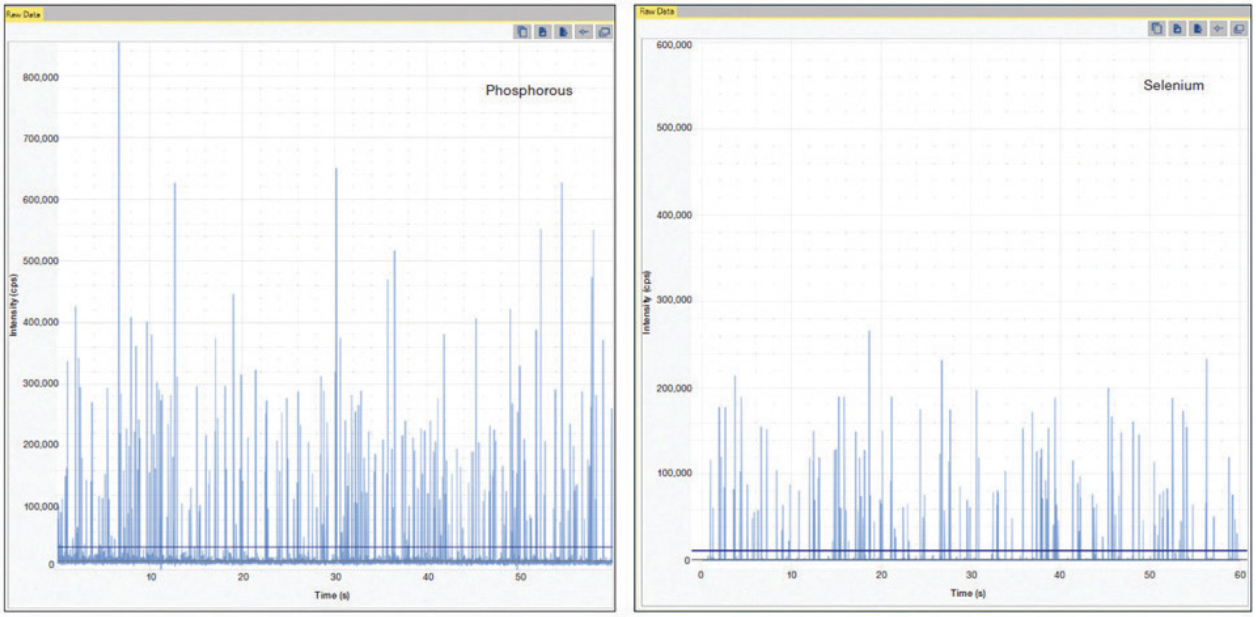


Figure 2. Raw data showing the measurement of P and Se in selenized yeast cells.

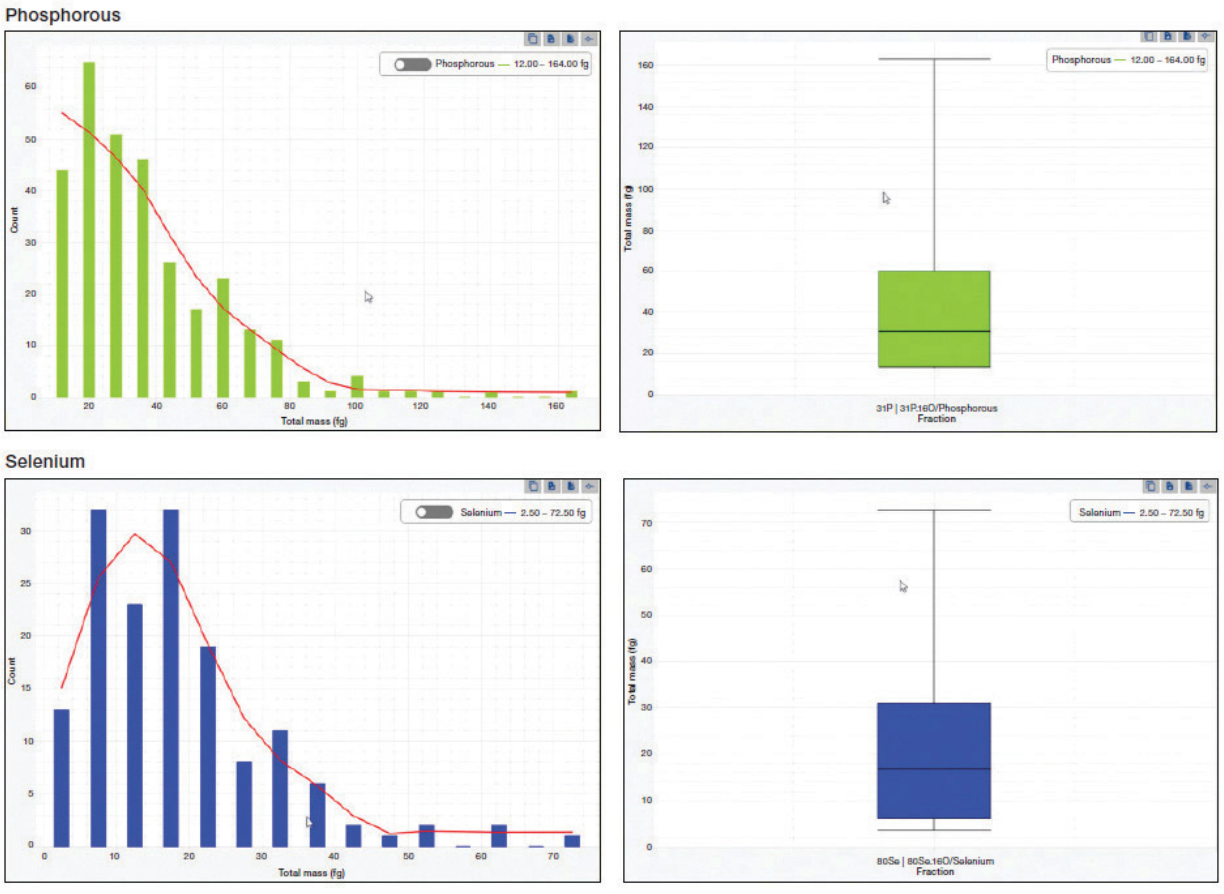
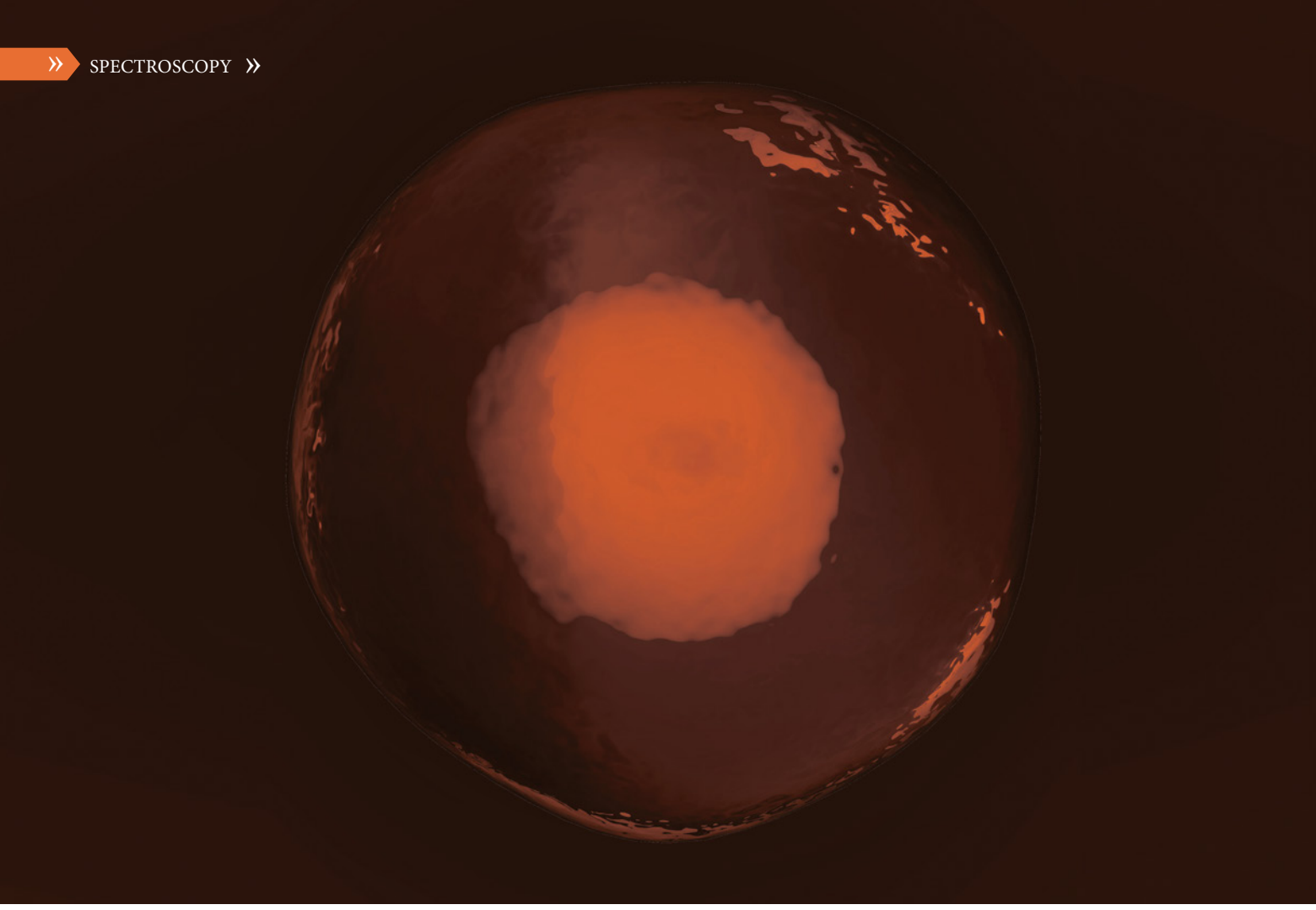


Figure 3. Mass distribution for P and Se in selenized yeast, left column shown as a histogram (bin size 8 fg for P and 5 fg for Se).



analysis of trace elements in single cells. Scientists can now accurately establish trace element mass per cell and the element distribution across a cell cohort.

However, this technique relies heavily on the right analytical software being in place so that detection and transport efficiencies can both be determined accurately, and a sequential approach can be used to measure multiple elements for identical periods on a single sample aspiration. With comprehensive data evaluation tools, both raw and intermediate data can then be utilized to enable full representation and analysis of the mass and number concentration data.

By using scICP-MS technology to detect trace elements at the single-cell level, analysts can gain a greater understanding of the migration and function of trace elements at a cellular level. Data such as these can be used in a variety of applications, perhaps for the development of more advanced therapies for a wide range of clinical presentations, better diagnostics for toxin ingestion or environmental pollution and even to improve quality and efficiency measures in bioproduction processes.

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About the Author

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What's Keeping Your Enterprise from Fully Leveraging Its Data?

Jim Olson

CEO
Flywheel

Research & development (R&D) processes are increasingly being redefined within the framework of digital transformation. With these initiatives, pharma organizations aim to improve speed to market and reduce the considerable R&D costs of drug discovery and development.

Artificial intelligence (AI) and machine learning (ML) are key parts of this transformation. However, organizations are discovering that harnessing these approaches isn't the work of just a few weeks or months. Some companies have gone through several iterations of digital transformation in R&D, with costly failures along the way. A recurring issue among these iterations has been the problem of how to efficiently de-silo data and enable enterprise-wide access.

Machine learning is data-hungry (especially for diverse data), and unless research enterprises have outstanding data governance models in place, they face challenges in realizing a true digital transformation. Often, the challenge is in breaking data out of institutional silos, uniting them in a central repository (or a centrally managed and normalized set of repositories), and standardizing them for machine learning.

Decades of ingrained culture, pieced-together tech stacks, and homegrown systems make strong headwinds for life science leaders as they seek to move their research teams forward. But the risks of the status quo are impossible to ignore: without modern data management, organizations are wasting money, missing innovative opportunities, under-leveraging their assets, and potentially even facing compliance risks.

Why Is Standardizing Data Such a Challenge?

It doesn't take long to understand at a high level why data management is so difficult for pharma companies. The data they hold are old and new, simple and complex, and sourced from multiple places, ranging from internal or external research results to clinical trials that are still underway. In addition to what is located in a company's own archives, data can be held externally by development partners such as contract research organizations (CROs) and clinical sites.

To explore just one example of the difficulty in standardizing even newly captured data, consider a global clinical trial with hundreds of patients that has prescribed an imaging protocol with five types of examinations for every patient at multiple time points. With imaging being performed via multiple sites, devices, providers, and languages, this trial could generate thousands of unique metadata tags and descriptions.

As this example illustrates, the sum of an organization's data, having been captured over time by different researchers, different devices, and using different organizational conventions, results in a collection of heterogeneous data with untold variation, even if data is provided in the same format (e.g., DICOM). The older the data, the more challenges may arise when attempting to curate those data. Over a dataset's lifecycle, as the data have moved through transfer and analysis pipelines and changed format, the likelihood that metadata have been manipulated or even removed increases. Significant portions of the data will likely predate AI/ML and will not have been acquired, archived or organized with such applications in mind. However, as already mentioned, ML is data-hungry, and even legacy data or data that are part of long-term longitudinal studies with issues like these are worth curating to create bigger datasets for training.

Traditionally, in order to harness disparate data for ML, research teams must spend countless hours locating datasets and manually curating them to a common standard. This curation entails tasks including selection, classification, transformation, validation, and preservation of research data and supporting material. The time required by this

manual curation process dramatically increases costs and time needed for discovery and development of therapeutics. Failure to implement a standardized process can even set up the enterprise to waste money again and again, finding and curating the same data repeatedly.

To avoid these problems, life science organizations must adopt strategies to efficiently curate data and associated metadata (in all forms) upon ingestion to a central repository. Without an established and diligent approach, researchers cannot efficiently leverage the enterprise's assets, and data that should be the fuel for development instead becomes a stumbling block.

Applying FAIR Principles to Complex Data

The data management framework that the ML research community has embraced in recent years is FAIR Data—meaning digital assets should be Findable, Accessible, Interoperable and Reusable. While the FAIR principles are more widely applied in academia and in clinical research settings (where data sharing is expected and required), they are also applicable within the walls of life science companies to make data more valuable across the enterprise.

Forward-thinking life science companies are using these guidelines to not only help combat the data management issues they are facing, but also to maximize the potential of their data. If applied correctly, the FAIR principles can advance research in pharma companies by reducing R&D work and costs, bringing operational efficiencies, and eventually accelerating time to market.

Of course, applying the FAIR principles is enough of a challenge when dealing with tabular data—FAIRifying the medical imaging data required for many ML efforts is an even bigger hurdle. Medical imaging is a rich and valuable source of information for researchers, but because of its large size and complex nature, these data pose one of the biggest challenges to organizations that are seeking to de-silo and FAIRify data.

As an example, consider DICOM files. The DICOM format itself provides some level of standardization, but significant variations still exist between modalities (MR, CT, PET, etc.), vendor instrumentation (Siemens, GE, Philips, etc.), acquisition type, and specific site. Such differences must be reconciled before the data can be used in assessment/analysis approaches, including ML.

Additional challenges standing in the way of leveraging imaging data include the sheer size, as data sets can be in the range of gigabytes per study, terabytes over a cohort, and petabytes in legacy systems. Furthermore, labeling the data often requires qualitative assessments by scientists and radiologists. Setting up workflows and data capture mechanisms for this work can add more labor to an already intensive effort. Moreover, imaging data oftentimes need to be integrated with other data types (i.e., clinical measures). Collectively, these factors help illustrate why application of the FAIR principles presents a high hurdle—even to very motivated research teams.

A Realistic Approach for De-Siloing and FAIRifying

Life science enterprises are coming to terms with the fact that manually locating datasets and curating them at the scale required for ML is cost-prohibitive, time-consuming, and prone to human error. As discussed, data and metadata from internal and external sources needs to be curated, including standardization, classification, and quality control, to ensure that it meets the standard required for complex analysis and ML workflows. As more data is introduced over time, these processes must be easily repeated within and across datasets, and scale with the size of the data coming in.

In attempts to streamline some of this work, many organizations have created homegrown infrastructure for select purposes. However, these systems are typically built for very specific tasks and require expertise from IT departments and/or data scientists to create and maintain. Such programs can be difficult to train staff on, and the institutional knowledge on how to run them may reside with just a handful of people, which puts such operations at risk when teams are reorganized or key members depart.

Many organizations are discovering that a better alternative is a modern data management platform, which can automate much of the work of ingesting data—even complex imaging data—and curating it to FAIR standards. The automation of these processes is key, as it reduces human error and variability. In addition, automation also promotes adoption of FAIRification as a realistic and achievable goal that doesn't require an indefinite all-hands-on-deck effort from data scientists.

A modern data management platform can leverage cloud scalability and parallelism to achieve many goals at once: It reduces upload time while handling data from both old and new sources. It automatically de-identifies data, extracts metadata, and classifies data per needs. It then builds an easily searchable collection of data. In summary, it prepares the data for downstream processes in a standardized and efficient way.

With this type of extensible data platform, the FAIR principles can become more concrete within an organization:

- **Findability** is dramatically improved, as researchers can build their complete dataset with simple queries within one interface. Without this approach, researchers commonly must request data from CROs, external collaborators, or an internal archive, which can take days or weeks, and often comes with additional costs (which are paid repeatedly if multiple divisions request the same data from the vendor).
- **Accessibility** is handled with role-based user permissions, which can be configured to give individuals the appropriate level of access to data, and user roles that enable which actions they can take with data.

Thinking of accessibility in another way, data access can also be improved between the enterprise and an external collaborator or CRO. With the right configuration, new data from an external collaborator or CRO can appear in the organization's catalog as it is captured, instead of researchers having to wait for the data to be delivered in a package at designated time points.

- **Interoperability** is simplified with APIs and tools for working with the data, including export, analysis and integration with other data types.
- **Reusability** is enabled by letting teams repurpose the same data for analysis and large-scale processing across the enterprise, which is easily possible if the data and associated metadata are well-described and stored.

Aside from the efficiency benefits that can be achieved from de-siloing data, organizations should also consider how modern data management can simplify compliance and regulatory approvals. First, de-identification tools can be configured to remove personal health information (PHI) and personal identifiable information (PII) "on the edge," before it comes into the platform and is made accessible to researchers, ensuring consistency across departments. Additionally, audit trails can be easily captured that show access logs, versioning, and processing actions.

With a centralized, standardized and scalable infrastructure that performs these functions, pharma research teams can enable FAIR-driven processes, meet their greater R&D goals, and plan for more ambitious data-driven objectives in the future. The ability to efficiently and securely access massive amounts of curated data on the cloud repeatedly can enable research that wasn't possible in the past. These tools allow R&D groups to meet project deadlines focused on processing large, complex objects with varying data formats in a standardized and reproducible (and repeatable) manner while not being burdened with manual data management.

By combining a sophisticated approach to data management with well-thought-out goals for complex analysis and/or AI/ML, organizations can avoid the pitfalls that have hindered digital transformations thus far. Scientists and researchers can focus on analyzing and processing datasets, rather than managing them—resulting in accelerated R&D and innovation to bring therapeutics to market faster.

Author Biography

Jim Olson *is CEO of Flywheel, a biomedical research informatics platform. The company uses cloud-scale computing infrastructure to address the increasing complexity of modern computational science and machine learning. Jim is a "builder" at his core. His passion is developing teams and growing companies. Jim has over 35 years of leadership experience in technology, digital product development, business strategy, high-growth companies, and healthcare. He has worked for large and startup companies, including West Publishing, now Thomson Reuters, Iconoculture, Livio Health Group and Stella/Blue Cross Blue Shield of Minnesota.*

Biopharmaceuticals and Biosimilars

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Catalent

Kaitlyn Vap
Life Sciences Lead Product Application Specialist
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Over the last year, other than the pandemic, what do you feel has been the major industry issue with respect to biopharmaceutical product development and manufacture?

Stacey Treichler, Director, Head of Marketing & Strategy, BioModalities, Catalent: We are seeing continued growth in multi-specific antibodies, for example bi-specifics, tri-specifics, and T-cell engagers. Results from multi-specifics in the clinic look promising, but there can be unique challenges associated with their development and manufacture. Those challenges range from upstream development (e.g., optimizing the cell culture conditions for high titer) to downstream development (e.g., ensuring purification of products with the correct chain pairing), and analytical development (e.g., developing potency assays that properly measure activity). As more of these molecules advance through the clinic, the industry is working on solutions around cell line development, purification, process, and analytical development to improve manufacturing efficiencies.

Kaitlyn Vap, Life Sciences Lead Product Application Specialist, Sievers: The pandemic has contributed to many industry issues around supply chain, time-to-market, regulatory scrutiny, etc.; however, outside of the pandemic, the data-insight gap continues to develop as a major industry issue for biopharmaceutical product development and manufacturing. This issue has evolved as the volume of data being collected in product development, manufacturing, and clinical settings continues to grow exponentially, but the capabilities of leveraging that data to make decisions, predict, diagnose, and optimize do not match that level of growth. Companies continue to operate with manual and siloed processes, which ultimately leads to isolated data that does not provide insight into process performance characteristics. With tools like machine learning, predictive analytics, and artificial intelligence continuing to emerge, it will be pertinent for the biopharmaceutical industry to adopt software platforms that allow for the integration of these tools for the purpose of optimizing drug development,

manufacturing, distribution, and clinical trial analysis. In doing so, the intent is to improve the time-to-market for life saving therapeutics without compromising patient safety or drug efficacy.

Looking at biosimilars - has their growth/approval rate met your expectations? If not, what has been holding them back?

Treichler: Various biosimilars continue to advance through the development pipeline in anticipation of innovators' products coming off patent. The uptake in the market has been variable and depends on the indication, and the policies that regulatory bodies have put into place regarding interchangeability and substitutions. One key challenge to a biosimilar gaining approval is proving its biosimilarity to the reference product (the innovator product). Another challenge for companies advancing biosimilar products is that upon launch, they are likely to need to compete for market share not only with both the innovator's product, but also with other biosimilars.

Vap: To date, 25 cell and gene therapies (CGT) have been approved by the FDA. Looking at the growth/approval rate in 2022, bluebird bio had two gene therapies approved – Zynteglo for treatment of patients with beta-thalassemia and Skysona for treatment of patients with cerebral adrenoleukodystrophy. Janssen also had a cell therapy approved in 2022 – Carvykti for treatment of patients with relapsed or refractory multiple myeloma. While three CGT approvals in 2022 is a small fraction of the 25 total CGTs approved, the industry is trending steadily and preparing to grow rapidly over the coming years. In the 2022 Prescription Drug User Fee Act (PDUFA) VII commitment letter, the FDA's Center for Biologics Evaluation and Research (CBER) calls for additional resources to support the increasing volume of CGT programs in the Office of Therapeutic Products (OTP). In 2023 they plan to hire 132 additional resources and another 48 in 2024. This level of resource recruitment comes in light of bluebird bio's two 2022 approved gene therapies and in preparation for an increasing amount in 2023, one of which may be Vertex and CRISPR Therapeutics' ex vivo CRISPR/Cas9 gene-edited therapy, exagamglogene autotemcel, for the treatment of sickle cell disease and transfusion-dependent beta-thalassemia.

Supply chain issues have affected every industry. Specifically, how has this issue impacted the biopharmaceutical market?

Treichler: The supply chain issues caused by the pandemic and other factors have led to inconsistency in the ability to source key raw materials and consumables, for example purification resins. Long lead times and stock outs can impact the ability to schedule manufacturing slots, which can delay production. To mitigate this risk, many companies have secured secondary supply sources, extended their buying horizons, and increased their inventory of critical materials. Some have also developed improved business analytics to identify and track potential supply risks earlier, giving them more time to respond to potential issues.

Vap: While supply chain issues have influenced drug development and manufacturing timelines, there have also been other ways in which the biopharmaceutical industry has been affected. Novel techniques to reduce the need for more starting material have been more widely adopted. Examples include plasmid amplification and polymerase chain reaction (PCR) based mRNA manufacturing. The latter of the two replaces a pDNA linearization approach to mRNA manufacturing, requiring a significant amount of starting pDNA and a master cell bank. To juxtapose the more novel methods to emerge from supply chain constraints, there has also been a resurgence of more traditional techniques to avoid the need for customized solutions that supply chains are struggling to support. An example of this is the use of CHO rather than HEK293 or SF9 platforms for the production of gene therapies. CHO platforms have been proven as a robust manufacturing method for monoclonal antibodies and many single use system vendors have the necessary equipment, packaging, and configurations for a CHO production system. While single use vendors also support HEK293 and SF9 platforms, sometimes these require custom solutions that strain the supply chain.

Briana Nunez, Lead Researcher, Sievers Instruments' Microbiology Center of Excellence: Supply chain issues have touched many facets of production in biopharmaceutical companies which impact the greater market. From validating alternates sources and vendors to increasing financial commitments to secure parts and materials, biopharmaceutical companies have been forced to become more dynamic. Customers in the biopharmaceutical markets have been forced to accept longer lead times which could potentially reduce the overall growth of their company.

Another issue that has been brought into focus by the pandemic is hiring and staffing. Has this been a problem for the biopharmaceutical industry? What can the industry do to alleviate this moving forward?

Treichler: Hiring and retaining staff has undoubtedly been a challenge in the biopharma industry these past few years. Biologic development and manufacturing requires workers to have a unique skill set, and it can be hard to find people who are already equipped with all the necessary skills for the job. Some of the ways that biopharma companies have tried to address this are by partnering with universities to train students in the skills they need when they graduate. It has been important too to develop robust internal training programs for new hires who may not have the full complement of skills they will need, and will, as with any fresh recruit, require training in a company's own individual culture, procedures and practices.

Vap: The biopharmaceutical industry struggled with hiring and staffing for some time before the pandemic as sectors within the industry such as cell and gene therapy were just beginning to grow out of their infancy. With that being said, historically there has only been a small fraction of individuals with the technical expertise necessary to excel in these fields, making it difficult to both hire and retain these individuals. There are now graduate programs specific to biopharmaceutical career paths along with experienced/seasoned individuals leading the effort to bring new cell and gene therapies to the market. Academic institutions operate similar to businesses in the sense that market demand needs to be present in order to pursue a business project, or in this case a degree field; therefore, in order to institute bachelor's degrees specific to a biopharmaceutical career path, younger populations need to be made aware of the biopharmaceutical industry and its function. In doing so, this has the potential to broaden the candidate pool for hires into the cell and gene therapy industry.

Hayden Skalski, Life Sciences Product Application Specialist for the Sievers Instruments product line at Veolia Water Technologies & Solutions: The biopharmaceutical industry has battled this issue since the onset of the pandemic, and it has not been resolved currently. High turnover rates made it extremely difficult for companies in this industry to retain talent, especially in growing fields like cell and gene therapy due to the rapid expansion of this sector and a growing number of opportunities. If companies are worried about retaining employees to get their products out to market on time, they can look for ways to automate processes in quality control and manufacturing departments. For example, there are numerous automated assays for critical release tests that require less training, thus alleviating some of the strain on staffing. As turnover rates continue to be a concern, companies seek to implement simpler, automated instruments where training for departments can be conducted in less than a day.

Looking ahead, where do you see the biopharmaceutical segment of the industry heading in the next five years?

Treichler: I believe we will see more complexity in the types of biologics that are being developed. Multi-specific antibodies, antibody-drug conjugates, and antibody fusions are just some examples of complex proteins that I believe will continue to take a larger share of the biologics pipeline. As these modalities become more complex, it will become increasingly important to continue to develop expertise, technologies, and processes that will enable efficient development, scale up, analytical capabilities, and manufacturing to bring these therapies to patients quickly.

Vap: The accessibility and affordability of biosimilars to the patient populations needs to be addressed. To confront this problem, biopharmaceutical development and manufacturing practices need to be more efficient to control the consistency and scalability of drug product. For this reason, the development and adoption of continuous manufacturing and integrated software platforms will likely be an industry focus over the next five years. Instruments, controllers, and data warehouses need to speak the same language to aggregate, analyze, and distribute data. Building in machine learning, artificial intelligence, and predictive analytic capabilities will be key to design agile operations with the ability to automatically diagnose failures and optimize processes. With these things in mind, it will be critical for vendors/suppliers to collaborate to enable technological advancement for the biopharmaceutical industry with the intent of driving efficiency gains.

Nunez: The biopharmaceutical industry will continue to drive progress in automation, not only for efficiency, but also for data integrity. Subjective testing versus objective testing does not require struggling with decisions. A shortage of laboratory personnel has also increased the interest in automation. The ability to manage many laboratories at once, while balancing the reduced number of analysts has created a need to lean out many repetitive tasks such as pipetting and counting plates to decrease worker burnout.

Skalski: As the industry looks for ways to reduce human intervention in many processes, it's safe to say that biopharmaceutical companies will be heading toward innovative automation and pharma 4.0 concepts. Automated processes allow users to maintain a state of control in their laboratories or manufacturing suites. Most often, with automation comes an increase in data connectivity. In order to lean out processes and reduce the potential for human error, companies must assess the capabilities of their processes to analyze data and predict/diagnose errors before they happen. Adopting new automated technologies and implementing processes that reduce the user footprint will be crucial in how the ever-evolving biopharma industry adapts in the future.

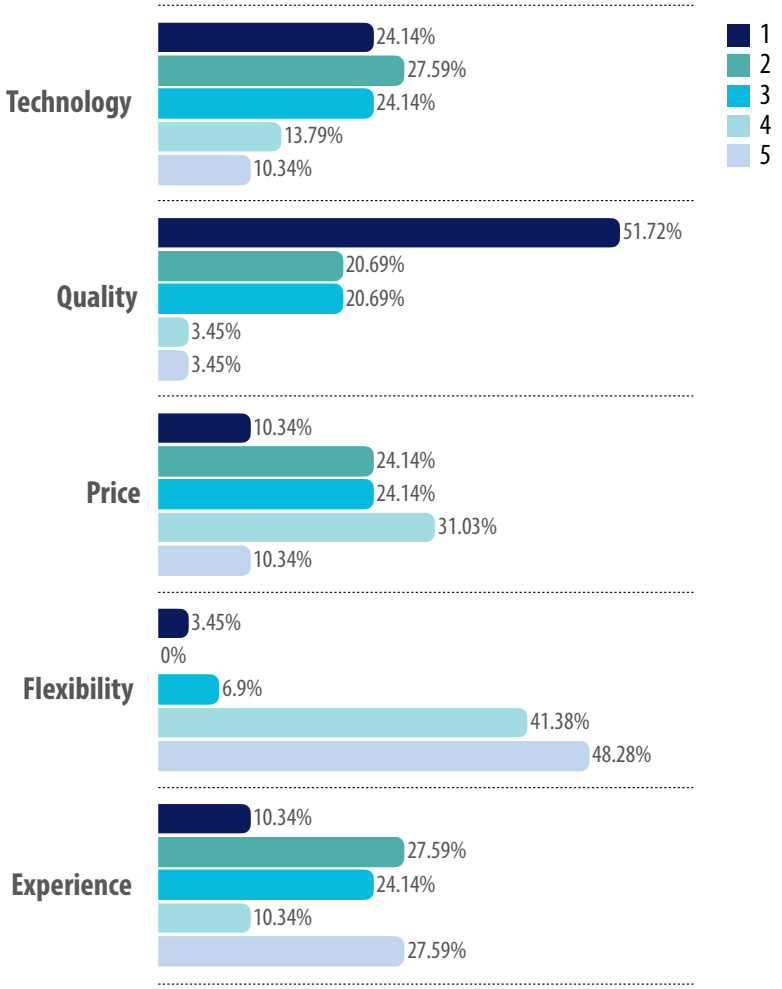
Drug Development & CDMO Survey

American Pharmaceutical Review recently conducted a survey of our readers to determine their thoughts regarding Drug Development & CDMOs. Please see the results of our survey below.

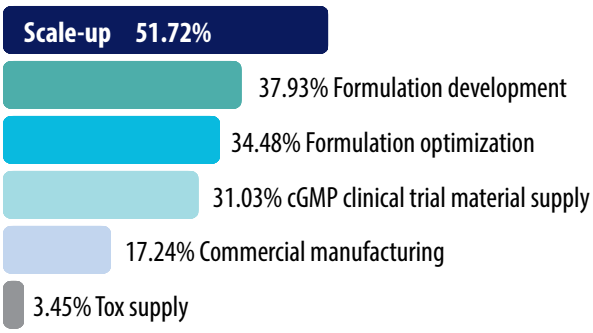
ASCENDIA PHARMA

Please rank the key factors when selecting a CDMO.

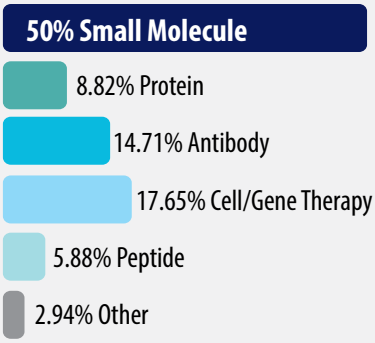
(1 – most important; 5 – least important)



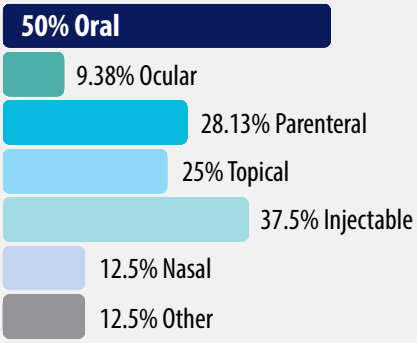
What is your current drug development need?



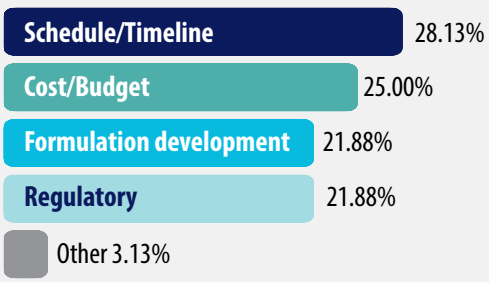
Please select the primary focus of your drug development pipeline.



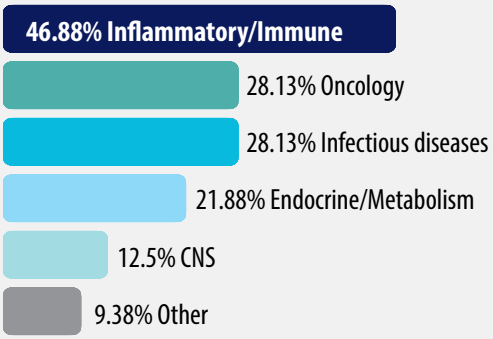
What kind of dosage types do you work with?



What is your biggest hurdle in drug development?



What disease area(s) will your next project to focus on?



Robotic Endotoxin Testing System

The Endosafe® Nexus 200™ is a data integrity compliant, fully robotic instrument, capable of processing both undiluted or complex, serial dilutions for water, in-process, and final product testing via Endosafe Limulus Amebocyte Lysate (LAL) cartridge technology in a fully enclosed system. Powered by Endosafe EndoScan-V version 6.1, the system allows for data to be exported into a Laboratory Information Management System (LIMS) integration and provides improved traceability, security, and data management on an integrated touch screen. The Nexus 200 combines technology, innovation, and control to optimize and streamline testing by combining the Endosafe LAL cartridge technology, the Endosafe® nexgen-MCS™ multi-cartridge system, and the Hamilton Microlab® Nimbus platforms for a low-maintenance, high-precision walkaway platform.

Charles River

www.criver.com

Case Packing Collaborative Robot

Company's collaborative robot (cobot) packing unit is a highly flexible platform that supports a variety of semi-automatic production modules, including case formers, print-and-apply case labelers, case layer inspection units, and case sealers. Ideal for loose or bundled bottles and cartons, the new cobot capabilities can safety and reliably pack up to 70% faster than manual loading. The enhanced cobot capabilities build upon the company's well-established Intelli-Pac system, known for offering high-integrity aggregation data when configured for a 'pack first, then inspect" process. Intelli-Pac enables operators to simply and expediently remediate out-of-spec products at the point of discovery, preventing costly downstream reworks and resulting in a process where cases are only sealed once satisfactorily aggregated. Versatile and vendor-agnostic, the machine permits brand owners to use their preferred serialization data management software and vision systems.

Omega Design Corporation

www.omegadesign.com

Prefilled Syringes With RFID-Labels

Schreiner MediPharm partnered with SCHOTT Pharma to develop a solution to equip prefilled syringes with RFID. Among other applications, the combination syringe and smart label opens up broad opportunities to optimize hospital routines. What differentiates the new RFID-Labels is the combination of conventional product information marking and the application of unique, digital identifiers for each unit. This enables optimized processes in hospital inventory management, patient care and documentation, as well as the digitial identification of medications and medical devices. In addition, digital first-opening indication to protect the integrity of the syringe can be incorporated.

Schreiner MediPharm

www.schreiner-medipharm.com

Fully Transparent Recyclable Mid-Barrier Blister Package

Recyclable in geographies where the #5 (polypropylene) recycling stream is available, the mid-barrier blisters feature a polyolefin blister film paired with a barrier PP lidding film. This marks the first time a formed blister + lidding combination is certified as recyclable– a significant milestone in the evolving push to make healthcare packaging more sustainable. From a manufacturing standpoint, initial machinability analyses have been positive, with large-scale tests scheduled for the near future.

TekniPlex Healthcare

www.tekni-plex.com/healthcare

PDA Parenteral Drug Association

pda.org/2023annual

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Inhaler Test Equipment

The Volume and Resistance Compensator (VRC) is designed for those pioneering the integration of abbreviated impactor measurements (AIM) into established workflows to streamline inhaler testing. For all orally inhaled products (OIPs), full resolution cascade impaction is a compendial method used to measure aerodynamic particle size distribution (APSD). AIM, in combination with Efficient Data Analysis (EDA), has potential to reduce the time and cost of such measurements, but comparability with full resolution measurements is important and not yet assured. The new VRC directly addresses this issue and is especially relevant for the testing of dry powder inhalers (DPIs). The VRC provides a robust easy-to-use tool that allows users to refine flow rate rise time profiles for AIM apparatus to ensure comparable conditions for aerosol generation allows volume and flow resistance to be independently varied is suitable for all types of AIM apparatus with successful matching demonstrated for both the Next Generation Impactor (NGI) and Andersen Cascade Impactor (ACI) and their AIM counterparts.

Copley Scientific

www.copleyscientific.com

Tangential Flow Filtration Purification System

The OptiMaxx tangential flow filtration (TFF) system, with four different sizes in the product line, ensures dynamic separation control in all applications and can be customized to the end-user's unique needs through its exclusive open architecture. With the ability to run two different pumps and two different flow rates simultaneously, OptiMaxx is truly configurable to meet the end user's TFF processing needs. Additional features include a customizable recipe configurator, an intuitive HMI touchscreen, and many filtration control schemes. The system allows users to configure process automation using multiple, pre-programmed ultrafiltration/diafiltration (UF/DF) phases, such as concentration, flush, and recovery, among many others. Furthermore, the open architecture enables users to choose from a variety of flow paths, filters and sensors, such as pressure, flow, temperature or conductivity.

High Purity New England

www.hp-ne.com

Cell Line Development Kit

The Gibco™ Freedom™ ExpiCHO-S™ Cell Line Development Kit allows users to generate cell lines suitable for clinical development without their own starter cells, vectors or prior experience in the field. The new kit uses Thermo Fisher's ExpiCHO-S cell line and a new powerful media platform specifically developed for it. The kit is based on a novel set of ProBioGen vectors equipped with strong promoters, selection markers and protective elements providing expression stability. Together with a simple workflow optimized by ProBioGen, the kit provides short development time, reproducibly high titers (3-5 g/L) and high expression stability.

ProBioGen

www.probiogen.de

Fully Automated Sample Preparation System

The new EXTREVA ASE Accelerated Solvent Extractor automatically extracts and concentrates analytes of interest from solid and semi-solid samples, such as persistent organic pollutants (POPs), polycyclic aromatic hydrocarbons (PAHs) or pesticides, in a single instrument, eliminating manual sample transfer for a walk-away sample-to-vial workflow. The system can also perform four sample extractions and concentrations in parallel, significantly improving sample throughput and laboratory productivity. With manual intervention significantly reduced by a factor of three, in some cases, results can be more accurate and reliable—allowing users more time to focus on value-added tasks. Analytical labs extracting from solid or semi-solid matrices can pair the sample prep instrument with gas chromatography (GC), GC-mass spectrometry (MS) or liquid chromatography (LC)-MS systems.

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- PROCESS TECHNOLOGY & INNOVATION
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Tommaso Biancalani, PhD, Genentech, Inc.

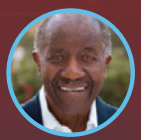
Preet M. Chaudhary, MD, PhD, University of Southern California

Steven M. Cramer, PhD, Rensselaer Polytechnic Institute

Rakesh Dixit, PhD, Bionavigen

Jeffrey J. Gray, PhD, Johns Hopkins University

Benjamin J. Hackel, PhD, University of Minnesota



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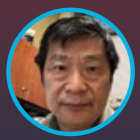
John Mattison, Arsenal Capital Partners



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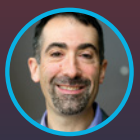

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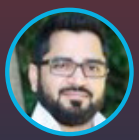

Sandeep Yadav, PhD, Sangamo Therapeutics

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Pharmaceutical P.I.N. POINTS
Patent Innovation News

The purpose of this column is to highlight and summarize recent key patents in the pharmaceutical arena issued by the US Patent Office in September-October, 2022.

Neelam Sharma, MS,
LakshmiLavanya Kundurthy, BE and
Hemant N. Joshi, Ph.D., MBA*

Tara Innovations, LLC
www.tarainnovations.com and www.tara-marketing.com
**hemantjoshi@tarainnovations.com*

Device and Methods for Endoscopic Patch Delivery;
A. Smith, A. Pic, and H. Rebar; Boston Scientific Scimed, Maple Grove, MN; U.S. Patent # 11,439,374; September 13, 2022.

Endoscopic procedures are performed for various reasons including – collection of tissue samples, mucosal resection and submucosal dissection. Such procedures can lead to wounds in need of repair. This patent claims a method of delivering a patch to the target site. It involves a patch in folded or crimped configuration, releasing the patch from the endoscope to the target site. The patch is at the distal end of the endoscope on a cap secured by a flexible band. Releasing the patch from the cap includes actuating a wire to cut the flexible band from the cap. The patch may comprise of a biomaterial such as chitosan or extracellular matrix and may be biocompatible and/or bioresorbable.

Ultrasonic Urinary Bladder Drug Delivery;
A. Geva and L. Kushkuley; Vensica Medical Ltd, Tel Aviv, Israel; U.S. Patent # 11478618; October 25, 2022.

The present invention relates to the field of intravesical therapy. Intravesical treatment is a method that allows direct transfer of drugs into the urinary bladder. It may involve several challenges and limitations such as non-effective penetration of therapeutic drug delivery to the bladder. The current invention is a kit comprising a urinary catheter with a first and a second longitudinal lumen. The first longitudinal lumen is disposed inside a balloon and configured to inflate the balloon. The second longitudinal lumen is disposed outside the balloon and configured to deliver a therapeutic fluid into the urinary bladder. Activation of one ultrasonic transducer in the urinary bladder causes cavitation bubbles to form in the therapeutic fluid adjacent to an internal surface of the urinary bladder, and little or no cavitation bubbles are formed in acoustic coupling medium.

Adjustable Dosing Delivery and Multi-Sectioned Drug Compartment;
D. Shahaf and I. Shichor; Sipnose Ltd., Israel; U.S. Patent # 11,471,618; October 18, 2022.

The present invention pertains to a system for delivering aerosolized substance to a natural orifice of the body. In the pharmaceutical and therapeutic areas, although nasal delivery is an acceptable delivery route, providing an adjustable dose to a specific need is always an obstacle. It is therefore needed to provide a system which can be optimized for efficient delivery of a substance to a target site. This device is for delivering a predetermined volume of at least one substance within a body cavity of a subject. The device contains a) a capsule for containing the predetermined volume of substances; b) a delivery end, having at least one orifice of diameter D, c) a valve mechanically connectable to the capsule- an active configuration and an inactive configuration; d) a fluid tight chamber. The capsule further contains at least one mixing mechanism that mixes the substances and the pressurized gas after the valve is reconfigured to the active configuration.

Drug Delivery Composition Comprising a Self-Assembled Gelator; J.M. Karp, P.K. Vemula, G. John, and G. Cruikshank; The Research Foundation of the City University of New York, NY and The Brigham and Women's Hospital, Inc., Boston, MA; U.S. Patent # 11,471,515; October 4, 2022.

This invention relates to low-molecular-weight amphiphilic gelators. These gelators self-assemble into various nano- and micro-structures in a wide range of organic and aqueous solvents. The gelators also have the capability to deliver drugs. This patent discloses drug-delivery compositions, methods of making prodrugs, and methods of drug delivery using a self-assembled gelator. The backbone of the gelator can contain a drug or prodrug, such as acetaminophen or salicin. Additional drugs or agents can be encapsulated in the gelator. Enzymatic or hydrolytic cleavage can be used to release the drugs.

Restoration of Tumor Suppression Using MRNA-Based Delivery System; J. Shi, M.A. Islam, Y. Xu, O.C. Farokhzad, and B. Zetter; The Brigham and Women's Hospital and Children's Medical Center Corp., Boston, MA; U.S. Patent # 11,458,153; October 18, 2022.

Loss and/or mutation of tumor-suppressor genes is a dominant force in tumor development and clinical resistance to a variety of therapies. Restoring tumor-suppressor activity in cancer cells is highly challenging and requires the design of a functionally improved tumor suppressor with unique therapeutic modality. Recently, chemically modified mRNA has emerged as an intriguing alternative to DNA-based gene therapy. The delivery of mRNA presents several potential challenges. The object of the present invention is to provide nanotechnologies, which can be used to deliver a therapeutic tumor suppressor mRNA or combinations of different tumor suppressor mRNAs for cancer treatment. Patent discloses compositions and methods for treating cancer that include administering a therapeutically effective amount of a tumor suppressor mRNA complexed with a delivery vehicle.

Oral Liquid Compositions Comprising Amlodipine Besylate and Methods of Using the Same; N. R. Bhatt and A. Kapadia; ECI Pharma, Fort Lauderdale, FL; U.S. Patent # 11,452,690; September 27, 2022.

Amlodipine is mostly available as tablets. Just recently, amlodipine suspension and solutions were approved. So far, liquid dosage forms were prepared by compounding tablets into a suspension and such formulations result in a variety of issues. The current patent claims an oral liquid composition comprising: 0.1 to about 1.9 mg/mL amlodipine besylate, about 5 mg/mL to about 90 mg/mL cyclodextrin, about 0.5 mg/mL to about 4 mg/mL paraben and water. The composition may further include a sweetener, a flavoring agent, a stabilizer, a coloring agent and a thickener. It claims that the volume of this oral liquid composition retains at least 90% of initial concentration of amlodipine after the formulation has been stored in a sealed container for six months at various storage conditions.

Aqueous Wound Healing Formulation; H. Spanjer, K.J. Rivera, S. Maida, J. Librizzi, and A. D'Ovidio; Advantice Health, NJ; U.S. Patent # 11,446,256; September 20, 2022.

Typical wound covers (textile or adhesive bandages) aim to stop bleeding, promote healing and prevent contamination to reduce risk of infection. These have many disadvantages, such as dust collection, contamination, difficult application to certain areas etc. Liquid bandages can eliminate some of these issues, but have issues of their own such as the presence of organic solvents, and toxic polymers, stinging sensation and harsh scent. This patent claims an aqueous formulation comprising a water-soluble polymeric material capable of adhering to skin and acting as a barrier to moisture but not to oxygen, and allowing water within the formulation to evaporate leaving a film covering the injured area.

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