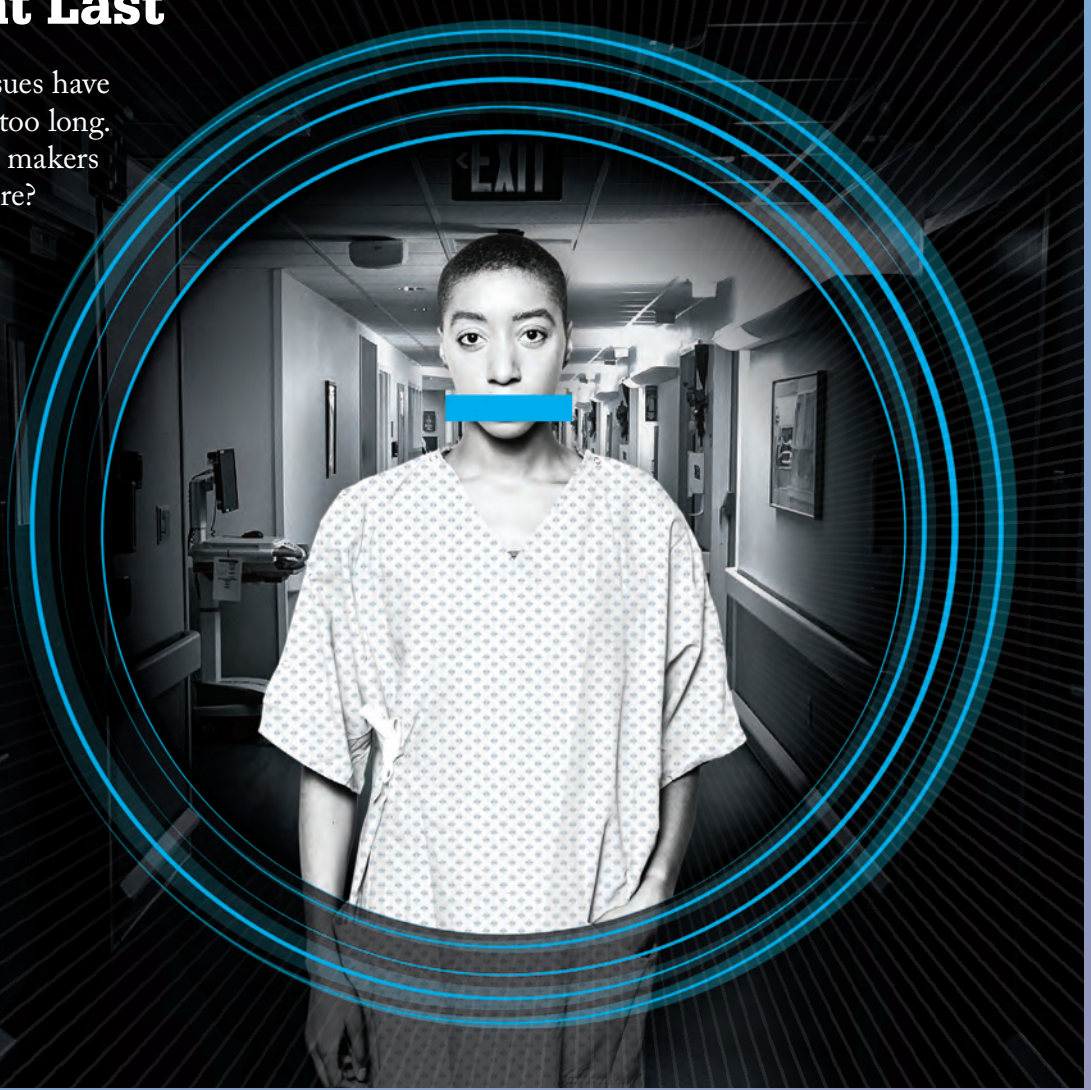
JULY / AUGUST 2022 # 86

the Medicine Maker®

A Voice at Last

Women's health issues have been neglected for too long. How can medicine makers ensure a fairer future?



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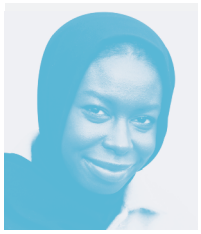
SARTORIUS

Lifting the Veil of Ignorance

From reproductive health to genetic disorders, the lack of attention given to women's health cannot continue



In 1971, American philosopher John Rawls devised a thought experiment, the "Veil of Ignorance," to explore human ideas on justice and society when people were stripped of the capacity to be self-serving (1). Subjects were asked to describe the types of societies they would choose to build without knowing the demographics of the people who would eventually live in them.

In the five decades since it was first proposed, many have come to the conclusion that societies should be fair and equitable to ensure the best outcomes for all. But in a world driven by self-interest, how easy is it to truly ensure equality – particularly in healthcare? In recent weeks, and in light of ongoing international childbirth pain relief shortages (2,3), this question has been on my mind.

Women have historically been left in the shadows of healthcare and pharmaceutical innovation. Though attitudes have certainly changed and women, particularly in Western nations, have better access to healthcare than ever before, there is still work to be done. The global shortage of epidurals is only a drop in the ocean of unmet women's healthcare needs. According to the WHO, 810 women die every day from "preventable causes related to pregnancy and childbirth" (4) – and, as a result of an endemic culture of violence in many countries, women fall victim to infectious diseases, mental health conditions, and the physical consequences of such acts – all of which require pharmaceutical intervention (5).

With so many opportunities to create meaningful change for these patients, it is difficult to understand why women's health – an area ripe with therapeutic promise – remains ignored by some in industry.

Though it would be unreasonable to suggest that the burden of finding solutions to the broad spectrum of women's health needs is for the pharma industry alone to fix, it's clear that the sector's interests align with supporting patient needs. Pharma companies can't realistically intervene in the decisions made by national healthcare authorities or prevent violence against women, but they can use their influence and connections to better engage with stakeholders and ensure that women have access to the best, most pertinent therapeutics possible.

In this issue's main feature, industry leaders share their views on the topic of women's health and what pharma is doing about it. Find the story on page 16 – and, if you have your own views to share on the topic, get in touch at maryam.mahdi@texerepublishing.com.

Maryam Mahdi
Deputy Editor

References

1. *K Huang et al., "Veil-of-ignorance reasoning favors the greater good," Proc Natl Acad Sci USA, 116, 23989 (2019). DOI: 10.1073/pnas.1910125116.*
2. *The Guardian, "'Difficult discussions' as NHS faces shortage of childbirth pain relief" (2022). Available at: https://bit.ly/3QNC8xg.*
3. *ABC News, "There's a global shortage of epidurals – and Australian hospitals are feeling the pinch" (2022). Available at: https://ab.co/3JViZHJ.*
4. *WHO, "Women's Health" (2022). Available at:https://bit.ly/3QNTOc8.*
5. *WHO, "Violence against women" (2022). Available at: https://bit.ly/2SxhJOU.*

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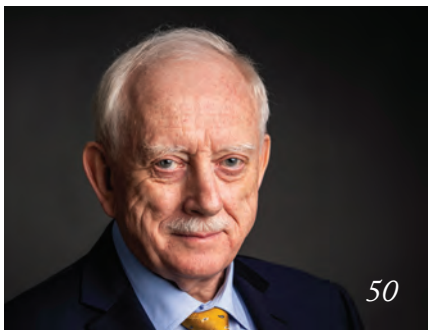

On The Cover

Exploring the areas of unmet need in women's health

Credit: Klaus Nielsen / pexels.com

Sandy Torchon / pexels.com

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Core Topics

Sitting Down With

the Medicine Maker

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60 Years of loving your cells

Celebrating 60 years of empowering progress in the bioprocessing industry

1960s

Grand Island Biological Company (GIBCO) founded by biologists Bob and Earline Ferguson after recognizing the potential of animal sera in research

Leonard Hayflick discovers the capacity for cells to divide in culture

First Gibco™ serum and dry powder media for scientific research produced

1970s

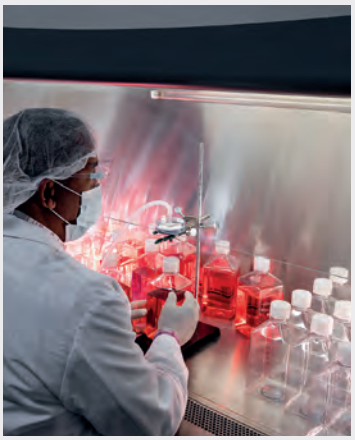
Approaches for deriving embryonic stem cells from early mouse embryos are identified

Researchers transition from glass to treated polystyrene vessels for cell culture

Rapid progression in the development of serum-free culture media

1980s

We begin to routinely assay fetal bovine serum (FBS) for its suitability in specific cell line applications



First custom cell culture media formulations are produced

Our products are used to support early cell therapy clinical trials

1990s

Gibco™ peptones widely adopted within the bioprocessing industry

Gibco™ liquid media concentrate technology becomes the first of its kind to be used in large-scale production

The chemically defined media revolution is begun by Gibco™ media

Learn more at **thermofisher.com/gibco60**

Thermo Fisher SCIENTIFIC

Founded in 1962 by Bob and Earline Ferguson, the Grand Island Biological Company (GIBCO) rapidly outgrew the garage in Grand Island, New York, where it began and has now become synonymous globally with innovative bioprocessing solutions.

Now part of Thermo Fisher Scientific, over the last 60 years, Gibco™ products and services have facilitated the achievement of many major milestones, including new manufacturing approaches and therapeutic modalities.

Join us in celebrating our anniversary as we look back at some of our highlights.

2000s

Proprietary Gibco™ Advanced Granulation Technology (AGT™) media format is made available

Chemically defined Gibco™ feeds and supplements are innovated and launched

Our iconic media bottle was designed to provide ergonomic features, improve its ease of use, and minimize contamination

2010s

The first Gibco™ Freedom™ cell line development kit is introduced

Gibco™ ExpiCHO™ Stable Production Medium, designed to simplify cell line development, is launched

The first CAR T-cell therapies, developed using Gibco™ Cell Therapy Systems (CTS™) products, are approved

2020s

Gibco™ High-Intensity Perfusion (HIP) CHO media for continuous perfusion bioprocessing, and Gibco™ Efficient-Pro™ Media and Feed system for streamlined monoclonal antibody production are released

Gibco™ multi-omics bioproduction services are launched

Gibco™ Bacto™ CD Supreme Fermentation Production Medium, a chemically defined and animal origin-free medium designed specifically to support high-cell-density cultures of Escherichia coli, is released

Our timeline does not end here

As the industry continues evolving, we are committed to pursuing continual innovation. This includes developing novel solutions for new and emerging modalities, such as next-generation vaccines and cell therapies.

Additionally, we are making $650 million of capital investments to proactively expand our global bioprocessing production capacity, helping us to shorten lead times and support our ability to meet global demand.

gibco

Upfront

Research
Trends
Innovation

Enter The Innovation Awards 2022

Nominations are open for our annual celebration of technology

We've already passed the midpoint of 2022 – and pharma is booming. mRNA is one of the biggest buzzwords of the year, with companies racing to accelerate the development and manufacture of this invigorated therapeutic class. We're also seeing a real push from technology and service providers in the field of cell and gene therapies. But which innovations are likely to have the biggest impact this year and beyond?

To find out, we're opening nominations for our annual Innovation Awards. In short, we're looking for any commercial innovation that is expected to shape the future of drug development and manufacturing – including (but not limited to) new manufacturing systems, software, formulation technologies, processing machines, expression systems, cell culture optimization approaches, reagent kits, chromatography systems, digital tools… To submit a nomination, go to: bit.ly/tmm-inv-2022

Please note nominations close on October 21, 2022.

How the nomination process works

All types of technology and equipment will be considered, but they must have been commercially released (or due for commercial release) in 2022. You need to provide the name of the innovation, the name of the company responsible, and a few details about why you think it deserves a spot in our 2022 Awards. Due to the volume of nominations, only successful nominees will be contacted.

A short list of the top innovations of 2022 will be published in December at which point you, our readers, will be able to vote on the technology that deserves to be crowned our grand winner.

The grand winner will have the opportunity to tell the story behind their innovation in an article to be published by The Medicine Maker in 2023.

If you have any questions, please contact the Editor: stephanie.sutton@texerepublishing.com

INFOGRAPHIC

Bill Cuts Bills

US pricing reforms are on the table, but which drugs will be affected? Here are some key facts and figures.

13 MILLION
Americans expected to save around
$800 PER YEAR
on health insurance premiums

10
Medicare to negotiate on the price of **10** drugs in **2026**; rising to **60** in **2029**

60

Sources
1. *Bloomberg, 2022. Available at: https://bit.ly/ph-drug-rfrm*
2. *Senate Democrats, 2022. Available at: https://bit.ly/3pVUMry*

BUSINESS - IN BRIEF

Making monkeypox vaccines go further, doing good in low-income countries, and the FDA's new inspection strategy…

- Supply of Imvanex/Jynneous – currently the only recommended vaccine against monkeypox – is limited but the EMA's emergency task force has found a way to make supplies go further. The vaccine is authorized only as a subcutaneous injection, but if it were delivered intradermally, it would require a smaller dose. The task force has advised that national authorities in the EU may decide to temporarily use the vaccine as an intradermal injection.
- Sanofi's nonprofit unit, Sanofi Global Health, has launched a brand called Impact that will see around 30 Sanofi medicines, including insulin, distributed in 40 low-income countries. The company is also launching an Impact Fund to support startup companies and innovators to deliver sustainable healthcare solutions for underserved regions.
- The FDA has published a report detailing its work to combat COVID-19. The report includes a variety of facts and figures around vaccine and drug development, as well as inspection activities.

Credit: Felton Davis / flickr.com

Of note, the agency says it is initiating a new inspection planning system that will be "more efficient, transparent, and adaptable to changing needs" – and that will help prioritize "high-impact inspections." The agency is also taking new actions to identify fraudulent products, including a proof-of-concept study for using handheld detection tools.

- Earlier this year, in March, the UK's medicines regulator approved AstraZeneca's Evusheld to prevent COVID-19 in people who have poor immune systems. Despite the thumbs up, it now seems unlikely the drug will reach UK patients before 2023. A report from the British Medical Journal claims that the government has said it will not purchase the drug because it is concerned it will not offer durable protection against the most dominant strain of SARS-CoV-2, Omicron. Evusheld has now been submitted to the UK's drug cost watchdog NICE to ascertain whether it offers value for money.

Open-Source Pediatrics

Researchers behind a side effect-searching algorithm for children's medicine have opened up their findings online

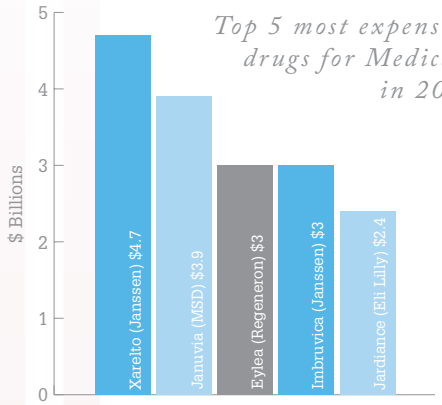
Researching drug side effects in children is a morally and technically fraught affair, which leaves useful knowledge and evidence somewhat scant. To get around the problem, academics at Columbia University have created an algorithm that applies predictive modeling to an FDA database of 264,453 pediatric reports to generate data on almost 20,000 possible forms of adverse drug events in children across all seven stages of pediatric drug development.

The researchers have shared their results on KidSIDES and the Pediatric Drug Safety portal (1,2) in the hope that other researchers can use them to confirm findings, aggregate further evidence, and follow up on signals they may observe.

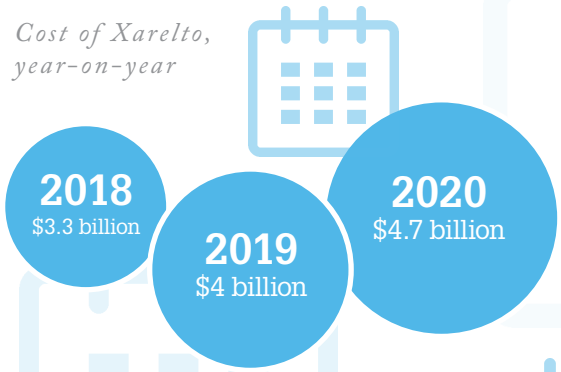
References

1. *PDS Portal (2022). Available at: https://nsides.io/.*
2. *PDS Portal (2022). Available at: https://bit.ly/PDS-ADE.*

Top 5 most expensive drugs for Medicare in 2020



Cost of Xarelto, year-on-year



Other companies that could be affected:

- Amgen
- BMS
- Takeda
- Pfizer
- Novo Nordisk
- UCB

Reform Crosses the Line

Democrats score a win in the US Senate for drug pricing controls

Drug prices have been in the US political spotlight for years – and so it was only a matter of time before action was taken. The US Senate has now passed the Inflation Reduction Act (by a vote of 51-50), which includes provisions around the climate and healthcare. Among other things, the bill will allow Medicare to negotiate prices for certain prescription drugs.

However, it didn't all go smoothly. Discussions between Democrats and Republicans were heated and some aspects of the bill were blocked, including a provision intended to cap insulin prices at $35 per month for private insurers. It failed to pass by three votes (although a $35 cap for insulin for Medicare patients remains intact).

Patients were quick to take to social media to express their disappointment about the insulin aspect of the bill, but pharma industry organizations are concerned that the government is interfering with the prices of medicines at all.

"Once the government can set prices for life saving medicines, it will demand even more control over the health care of American patients and the collateral damage from this bill will only grow," said a statement from PhRMA's President and CEO, Stephen Ubl. He also went on to describe the reforms as "a tragic loss for patients" that made "a litany of false promises" and could, ultimately, harm innovation.

Michelle McMurry-Heath, president and CEO of BIO, was also concerned. She said: "While we have frequently voiced our support for the Part D out-of-pocket cap included in the bill, we have also repeatedly warned of the policy's drastic and unnecessary blow to cures and therapies. Its passage today has built new barriers to battling current and future deadly pandemics, health inequality, and finding treatments for rare and hard-to-treat diseases."

We'd love to hear what readers think of the bill and the impact it could have on the pharma industry. If you're inspired to put pen to paper on the topic then email stephanie.sutton@texerepublishing.com.

Delving into Biopharma Trends

Free report from NIBRT and The Medicine Maker

Since 2017, The Medicine Maker and NIBRT have collaborated on the annual Biopharma Trends report. The goal? To give readers an insight into the trends shaping the biopharmaceutical manufacturing industry. Through a series of interviews, the 2022 report explores the views of leaders from across the biopharma industry – including Maik Jornitz (G-Con Manufacturing), Igor Splawski (CureVac), Jan Van de Winkel (Genmab), Fabian Gerlinghaus (Cellares), Rick Bright (The Rockefeller Foundation), and more.

As you may expect, a key discussion point for our leaders was the COVID-19 pandemic and its long-lasting effects on the industry and its supply chains. Other popular topics include the continuing excitement around cell therapies, advanced manufacturing methods, and the need to address skills shortages in the sector.

You can download the report for free at http://tmm.txp.to/nibrtreport

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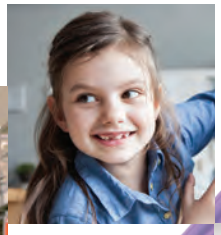
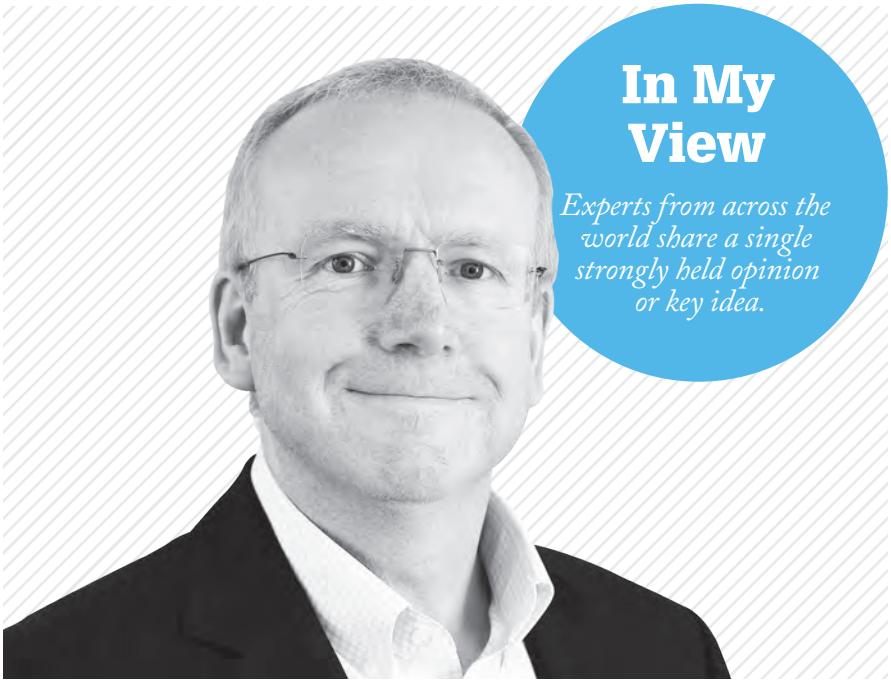




Green Progress and Pitfalls

Where are pharma companies falling behind when it comes to the environment?

By Michael Earl, Director of Pharmaceutical Services, Owen Mumford

Historically, the pharma industry has been a heavy polluter. One notable study found that pharma's emissions intensity (a metric to fairly compare companies of different sizes) exceeded the automotive sector by 55 percent, despite being 28 percent smaller as a market. The study concluded that to meet targets outlined in the Paris Agreement, the industry would need to see a 58.6 percent reduction in 2015 emission levels by 2025 (1).

And the good news is that progress is being made in a number of areas – namely, air emissions, waste, water, and energy usage. However, an analysis by Owen Mumford Pharmaceutical Services of the top 25 companies reporting environmental, social, and corporate governance (ESG) scores found three critical issues that have yet to receive sufficient attention. Firstly, efforts to reduce packaging in the industry are well behind other industries. Secondly, addressing contamination through antibiotic manufacturing emissions must be a priority (particularly as endeavors to combat antimicrobial resistance become increasingly difficult). Thirdly, there is a large variance in sustainability performance across businesses in the industry. Let's look at these three areas in more detail.

Packaging in the pharmaceutical industry has been largely focused on safety and sterility, making efforts to move towards sustainability challenging. Though policies to improve packaging are in place in most companies included in the analysis (76 percent), hard targets have been set by just 13 percent. Other industries are advancing faster in this respect; for example, McDonalds plans to use completely renewable and recycled packaging as soon as 2025 (3). Where clinically feasible, the industry can convert to sustainable alternatives – ensuring that there is a net environmental gain when changing original materials. One sustainable alternative is polyolefin laminate packaging, which is 70 percent recyclable and can be used for unit dose packaging of solid formulations. There is also a commercial benefit; adopting this packaging can lower packaging-associated costs by up to 60 percent (4). Reducing weight and improving packing efficiency can also reduce shipping resources and cost.

Contamination is a more challenging issue; 84 percent of companies analyzed have a policy on pharmaceuticals in the environment (PiE), and 36 percent on antimicrobial resistance (AMR). However, there is a lack of hard targets being set to enforce action. AMR has been identified by the United Nations Environment program as one of the greatest threats to global public health (5). In some countries, such as China and India, where there is a high level of pharmaceutical manufacturing, uncontrolled discharges can leak into water systems, consequently impacting the people and animals that come into contact with the resulting resistant bacteria. One study analyzed waste from a wastewater treatment factory in India and found concentrations of broad-spectrum antibiotic ciprofloxacin sufficient to treat 44,000 people daily (6). The complexity of tackling contamination could be one reason for slow progress in this area to date. But the longer the issue is not properly addressed, the more difficult it will become to solve. Responsible and informed policies are urgently needed.

Finally, the industry as a whole does not have a consistent approach to sustainability. Our study found a variance of over 40 percentage points between those committed to sustainable practices and others who had yet to make real inroads. Neither geography nor size seem to affect a company's ability to achieve impressive sustainability scores. One analysis shows that, despite selling similar products and generating similar revenues, one pharma company's CO2 emissions were five times greater than an industry counterpart (7). To that end, corporate will is just as important as a large budget. A further issue is that companies are not necessarily reporting progress in a standardized manner – an inconsistency that confounds tracking of progress and could be contributing to the high levels of variance we are currently seeing.

It's not all bad news. And we should acknowledge the efforts made by the pharmaceutical industry in other areas. A study by EcoAct analyzing top firms'

sustainability commitments showed the pharmaceutical industry performed well compared with many industries, with an average score of 60 percent – comfortably above the overall average of 53 percent (8). Our own analysis shows that 70 percent of companies are pursuing targets to reduce air emissions, and 50 percent of companies are setting hard targets to optimize water use – a positive development for an industry that is a major consumer of water (9).

But the goal of sustainability is a multifaceted challenge – and a little success cannot lead to complacency. The sizable environmental impact of the industry means there is still plenty of work to be done. Hard targets ensure firms are taking action and remain accountable. These targets must be continually scrutinized and updated in a bid to set ambitious industry standards and motivate every player in the supply chain to make greater strides. At Owen Mumford Pharmaceutical Services, we have already made significant steps, such as becoming one of the first medical device manufacturers globally to receive a B Corp certification. We recognize the importance of ongoing action, and our next ambitious targets include achieving net zero carbon emissions by 2045.

See references online at: tmm.txp.to/pharma-green

Securing Supply: Best Practices for Critical Raw Materials

COVID-19 has taught us that unexpected events can cause significant supply chain disruption – and there's no better time to consider secondary and tertiary sources

By Michelle Ferreri, Director, Custom Products, at Thermo Fisher Scientific Biologicals and Chemicals Division

As demand for biopharmaceuticals continues to increase, expanding manufacturing capacity to maximize productivity is key. However, increased production capacity necessitates more raw materials.

Though meeting scale-up needs or increasing sales volume may be possible with a single supplier, finite capacity or limited availability can make it difficult for the supplier to meet high demands for raw materials. As a result, many biopharma manufacturers are beginning to leverage secondary and tertiary suppliers of critical raw materials, such as cell culture media. In fact, qualifying additional suppliers may be essential for manufacturers to simply maintain capacity in the event of unforeseen circumstances. For example, halts in production due to failed inspections or facility shutdowns can directly impact the availability of critical raw materials. Global issues – such as SARS-CoV-2-related supply interruptions and shipping constraints – can also limit supply. Whether a manufacturer is looking for a supplier to increase its output or as a secondary source in times of need, securing multiple suppliers is a crucial step in keeping production on track.

When it comes to securing suppliers, manufacturers must successfully qualify the supplier and confirm they can meet their requirements. Ideally, this should be done proactively ahead of a critical need.

What to look for in a potential supplier

The first step in selecting an additional supplier is identifying those that can support your specific requirements. If you are looking for a media supplier to manufacture your media formulation, this may mean that you need one who can source the 100 components that make up your formulation and manufacture it in-house. Conversely, you may be looking for a supplier who can supply a small number of specific raw materials so you can manufacture your own medium. Understanding your requirements will streamline the selection of a secondary supplier.

Working with a media supplier who has qualified multiple sources is also an ideal approach to improve access to critical raw materials. Global suppliers typically procure raw materials from several different sources, creating secondary and tertiary supplies of their own raw materials in-house. For instance, a supplier would have a primary supply of a critical raw material, such as trypsin, but would also have qualified additional suppliers in case of a problem with their primary source – such as low quality or supply interruption. The materials from all these suppliers would have undergone the same testing to confirm quality and establish redundancy.

Considering the origin of your media supply is also important when selecting a supplier as it can help alleviate supply concerns while maintaining production. For instance, does a potential supplier have one facility that produces one of your critical raw materials? Or is it redundantly manufactured at multiple facilities across the globe? The latter helps safeguard the supply of your critical raw materials, even if supply shortages or shipping challenges occur.

A growing industry combined with potential instabilities in global markets

means that media suppliers are also acutely aware of how important it is to be able to supply products confidently and continuously. As such, many suppliers are investing in expanding capacity and volume to meet this demand, ranging from large investments (for example, construction of new facilities with increased capabilities) to more minor investments (for example, improving internal processes). Ultimately, these improvements are helping to increase the volume and reliability of raw material supply to meet increasing demand.

After a supplier is selected, how do you qualify them?

Though the qualification process for new suppliers may differ depending on the specific needs of a project, process, or company, several key steps help streamline the process.

i. Confirm quality. First and foremost, when qualifying a new supplier, you need to confirm the quality of the products you are procuring. You'll want to ensure your media supplier strictly follows its own best practices and has an established standard operating procedure to confirm the quality of their raw materials.

   Though suppliers have their own qualification requirements, it is still important for you to confirm this quality. Establishing your quality audit process is important; your specific requirements may differ from other companies.

ii. Confirm that specific processes or protocols are followed. After confirming the quality of the raw materials provided by a secondary media supplier, it is also important to confirm that any required processes or protocols are followed. For specific raw materials, this may range from confirming segregation of animal origin and animal origin-free products in-house to confirming the milling techniques used to create dry powder formats. If you are qualifying a supplier for the manufacture of your formulation, it is important to audit and qualify the specific manufacturing process, as well as the raw materials. Walking through how your medium will be manufactured in-house during a site visit is recommended. Such visits can be an important step in alleviating any concerns and confirming the techniques and equipment used are standard and appropriate for your needs. Finally, though site visits are important, virtual site visits have been gaining popularity as a suitable alternative.

iii. Confirm the accuracy of your products. Whether you are qualifying the production of a complex formulation from your secondary media supplier or a handful of critical raw materials, it is also important to test the products and confirm their identity. For many manufacturers, a documentation packet, such as a certificate of analysis, may be sufficient. However, depending on your requirements, a more in-depth audit of finished goods may also be necessary before qualifying a new supplier. Identity testing multiple lots of a medium formulation or going through individual raw materials, pulling batch records, and analyzing the documentation to confirm quality may be important to qualify your product.

iv. Confirm site-to-site equivalency. Site-to-site equivalency should be clearly demonstrated by media suppliers. Oftentimes, equivalency begins with procedures and practices around the supply chain and includes processes for quality management system alignment and harmonization, manufacturing, and equipment equivalency. Batch testing across the network should also be performed by manufacturers to confirm equivalency. Equivalency documentation or an audit may be sufficient to accept a material produced at multiple sites. Conversely, you may require multiple batches of a given product to demonstrate that the same product being manufactured at different sites performs equivalently in your process. Site visits may also be performed to confirm equivalency within a global network.

v. Confirm supply chain reliability. Though this is not strictly a necessity, when it comes to the qualification process, confirming the reliability of your new media supplier's supply chain is advisable. Evidence of a dependable supply chain should be provided upfront alongside discussions of any specifics of what will be provided. Though you may have already done this with a primary supplier, confirming with a secondary or tertiary supplier is just as important – whether they will be supplying raw materials in tandem with your primary supplier or only when the need arises.

vi. Establish transparent communication. Establishing a transparent communication system to share data is critical – from being alerted to supply updates or changes to any necessary quality documentation or paperwork. Ultimately, these systems can help keep things running on schedule and identify any potential issues.

Do not wait until it is too late

Given the increase in global demand, it has never been more important to consider whether qualifying additional suppliers is necessary to support the uninterrupted production of your essential biopharmaceutical products. Proactively qualifying additional media suppliers ahead of a critical need can mitigate the risk of costly delays to your process – all while supporting your ability to provide life-changing therapeutics to the people who need them most.

Veranova: Leading the Way in Synthetic Chemistry

As new treatment modalities emerge, drug developers are turning to synthetic chemistry – and partners like Veranova

Veranova is a global leader in the development and manufacture of APIs, focused on specialist niches with expertise in highly regulated and complex chemistries. Formerly part of Johnson Matthey, the company has over 50 years of experience navigating the challenges of the global healthcare industry and nurturing long-standing, trusted customer relationships. Operating within two divisions, Generics and Originators, Veranova delivers a differentiated service offering to pharma and biotech customers for every stage in the drug development lifecycle. Here, we speak with Garrett Dilley, Global Commercial Senior Director, to learn more about the company and the increasing demand in the pharma industry for synthetic chemistry expertise.

What is your role at the company and what inspires you?

I lead the Global Business Development team for our originator business. What inspires me about my day-to-day activities is that we get to help our clients and partners solve unique challenges, and work with them to transform their molecules into drugs.

For me, it's incredibly gratifying to watch and be a part of the evolution from development to medicines, and to see these treatments go on to help patients across many different disease areas.

What trends in new drug modalities are contributing to the need for synthetic chemistry expertise?

We've witnessed the emergence and continuing development of new treatment modalities, including innovative drug conjugate classes, such as antibody-drug conjugates (ADCs) and polymer-drug conjugates (PDCs), which balance selective targeting molecules with payloads for novel therapies. Also, there are proteolysis targeting chimeric (PROTAC) technologies, designed to degrade target proteins. These require the construction of specifically designed small molecules, which is best done using synthetic chemistry.

What other drug development challenges do originators face and how can synthetic chemistry help?

In my view, originators need to manufacture complex small molecules to meet well-tuned characteristics and requirements, such as bioavailability and efficacy. For this, synthetic organic chemistry solutions provide the method of choice for both their flexibility at the design stage as well as their precision at the production stage.

What is the story behind Veranova's legacy – and what expertise does the company have with synthetic chemistry?

Legacy is a great word to use. As you may know, Veranova launched as an independent company in June 2022 following its acquisition by Altaris Capital Partners from Johnson Matthey. Although technically a new company, Veranova's heritage and track record of excellence in synthetic chemistry enabling pharmaceutical development and manufacturing goes back to our pioneering work in the discovery and manufacture of platinum-based anti-cancer drugs, such as cisplatin and carboplatin, in the 1970s. Since then, we've expanded our breadth to encompass a wide array of small molecule therapeutics and supporting technologies.

What types of challenges is the company well positioned to help with?

At Veranova, we're combining our tradition of scientific excellence with a proactive and agile approach, ensuring that we're able to solve our clients' most challenging problems in the evolving development and manufacturing landscape for specialist and complex APIs. These include the aforementioned novel modalities, ADCs and PDCs, as well as highly potent molecules and controlled substances. This has led us to work with our customers and partners on tackling challenging purifications with, for example, preparative to production scale chromatography, and overcoming the hurdles of challenging isolations with our expertise in cocrystal formation and crystallization development.

Finally, as the industry continues to adapt to the increasing number of poor water-soluble molecules in the pipeline, we're combining our solid form and particle engineering expertise with detailed research to find bioavailable and unique physical forms of API.

Why is it important to work in partnership with your customers?

We work closely with our customers, establishing collaborative partnerships with open communication and understanding their concerns and their broader objectives. This is very important as it is through the trust that is established, our customers come to rely on us and consider us as an extension of their organization.

At Veranova, we provide our customers with the unique combination of a long heritage in drug development. This heritage, drawn from our experience over many years within a large multinational organization, is matched with the agility and customer focus we bring as a nimble organization focused exclusively on drug development and manufacturing.

By Maryam Mahdi

Overlooked and underserved. Regardless of age, ethnicity, or location, women's health needs remain relatively unexplored territory for pharmaceutical companies. It's an area of healthcare that is ripe with opportunity, but one that the industry still shies away from.

But why? Although the answer may not be entirely clear, we take a good stab in the dark with the help of industry experts, while trying to answer the most pressing question: "What must change?"

BREAKING THE SILENCE:

women's health under the lens

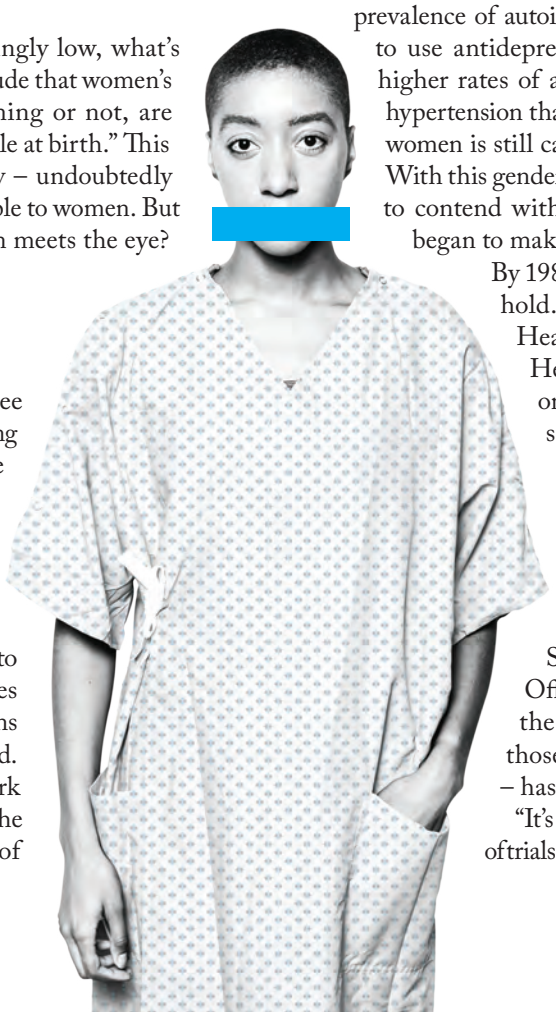
A HISTORY OF MISSED OPPORTUNITY

Decades' worth of exclusion has resulted in a knowledge gap in the women's health sphere. But as pharma companies reevaluate their approach to medicine making in this area, they will have to acknowledge the past that has contributed to the current R&D outlook.

For centuries, societies worldwide have been governed by patriarchal standards. Walls were built up and maintained to protect the rights and liberties of men, but not without cost. As societies change and as people actively choose to dismantle these longstanding biased frameworks, it is inevitable that some remnants of past inequality will take more time to address and, ultimately, erase – the impact on women's health being just one.

"In dollars, only one percent of the approximated US$200 billion spent on healthcare research and development focuses on women's health (1). As a result, half the population is left behind the health innovation curve," says Sabrina Martucci Johnson, Chief Executive Officer at Daré Bioscience and women's health advocate.

Even though the figure is shockingly low, what's worse, she says, is the prevailing attitude that women's health issues, whether life-threatening or not, are "simply a part of being assigned female at birth." This attitude – and its roots in misogyny – undoubtedly impact the therapeutic options available to women. But could there be more to the issue than meets the eye?



Thalidomide – a scandal with lasting implications

Despite the thalidomide scandal (see Notes on a Scandal on page 22) occurring over 60 years ago, for decades, it set the tone for pharmaceutical R&D across women's health indications. The documented safety risks that the drug posed to infant lives as well as the mounting public concern at the time meant that the floor was open to governments and regulatory agencies to respond. But some of their reactions could only be described as heavy-handed.

"The thalidomide scandal is a stark reminder that evaluating not only the effectiveness but also the safety of drugs in women is critical, particularly in women of reproductive potential," Johnson says. "This is certainly something that the FDA takes seriously when evaluating the risk/benefit potential of a particular drug."

However, in 1977, the agency made a decision that would help shape the way pharma companies would view women's medical issues for years to come. The agency published guidelines that prevented women of childbearing age from participating in clinical trials. Though well-intentioned, the decision affected attitudes on a broad scale (2).

"A mindset took hold in the industry that it would be easier to find out whether a medication was effective and safe if we didn't have to assess it in the setting of a fluctuating hormonal milieu (and its potential effects on absorption, metabolism, and excretion of the drug), and to a subject who might potentially harbor an early, as-yet undetected pregnancy; thus, the attitude became 'let's just study it in men for now, and get to the women after approval,'" says Gary Shangold, Chief Medical Officer at Enteris Biopharma.

However, the seeming convenience of excluding women from trials left a gaping hole in the industry's collective understanding of the ways medicines worked in women. "Women have a higher prevalence of autoimmune diseases and are more likely to use antidepressants. They also have significantly higher rates of arthritis, osteoporosis, diabetes, and hypertension than men. And the number one killer of women is still cardiovascular disease," Shangold says. With this gender-based disparity in disease prevalence to contend with, regulators and other stakeholders began to make a change to existing guidance.

By 1985, a new mindset was starting to take hold. A report published by the Public Health Service Task Force on Women's Health Issues challenged existing ideas on clinical trials and pushed industry stakeholders to consider how they could be made more inclusive (3).

In the years since, there has been a drastic change to the way clinical trials run – with more women represented than before – but the gender imbalance still remains. For Stephanie Seremtis, Chief Medical Officer of Haemophilia at Novo Nordisk, the exclusion of women – particularly those with the potential to birth children – hasn't completely disappeared.

"It's interesting yet horrifying that two-thirds of trials are still made up of men. With only a third

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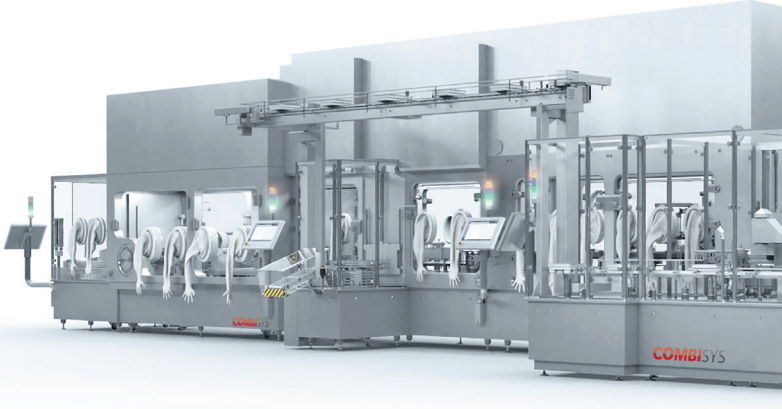

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represented by women, it's no surprise that women of childbearing age are not included," she says. "People have often theorized that women are afraid to participate but there is a clear history of exclusion."

This exclusion, she goes on to explain, runs across racial and socio-economic lines affecting a variety of marginalized communities. Inappropriate access to trials coupled with a lack of understanding of the barriers to participation mean that women from a variety of backgrounds remain excluded.

The traditional approach to clinical trials, Shangold argues, is one of the major reasons that fewer women choose to participate. For example, the numerous investigational site visits associated with these trials make them unattractive. He says, "It's one thing if a patient has a day job with site visits. However, add to that the responsibilities that have been traditionally owned by women in a family unit – for example, childcare and the provision of food – and the added burden of attending regular study visits can easily become too much of a time and energy challenge for a woman, whose alternative to participating in a clinical research study might otherwise be to simply take a known and safe, physician-prescribed medicine."

"Not only is women's health a therapeutic sector where innovation and fairly priced therapeutic interventions can do social good, but it's also a compelling value proposition."

Another challenge? The frequent use of placebo controls in late-stage clinical trials. "There is a 25–30 percent chance of being assigned to a group destined to be treated with a non-effective control," says Shangold. "Though I am a proponent of the value of placebo-controlled designs in many settings, it still creates an additional challenge to recruitment."

Pharma often purports that it aims to become more patient-centric and inclusive. But with many still left out of the equation when it comes to R&D, the industry will have to ask how it can move away from traditional trials and encourage more women to participate.

New approaches to old problems

By offering patients the opportunity to participate in trials without a significant loss of time and resources, decentralized trials are growing in popularity. As the name suggests, decentralized trials are not confined to specific sites and take place on digital platforms. Any patient with access can, therefore, take part.

"Anything we can do as an industry to make clinical trial participation easier can enhance engagement in the drug development process – minimizing visits, using virtual visits, and electronic diaries are all part of the solution," says Johnson.

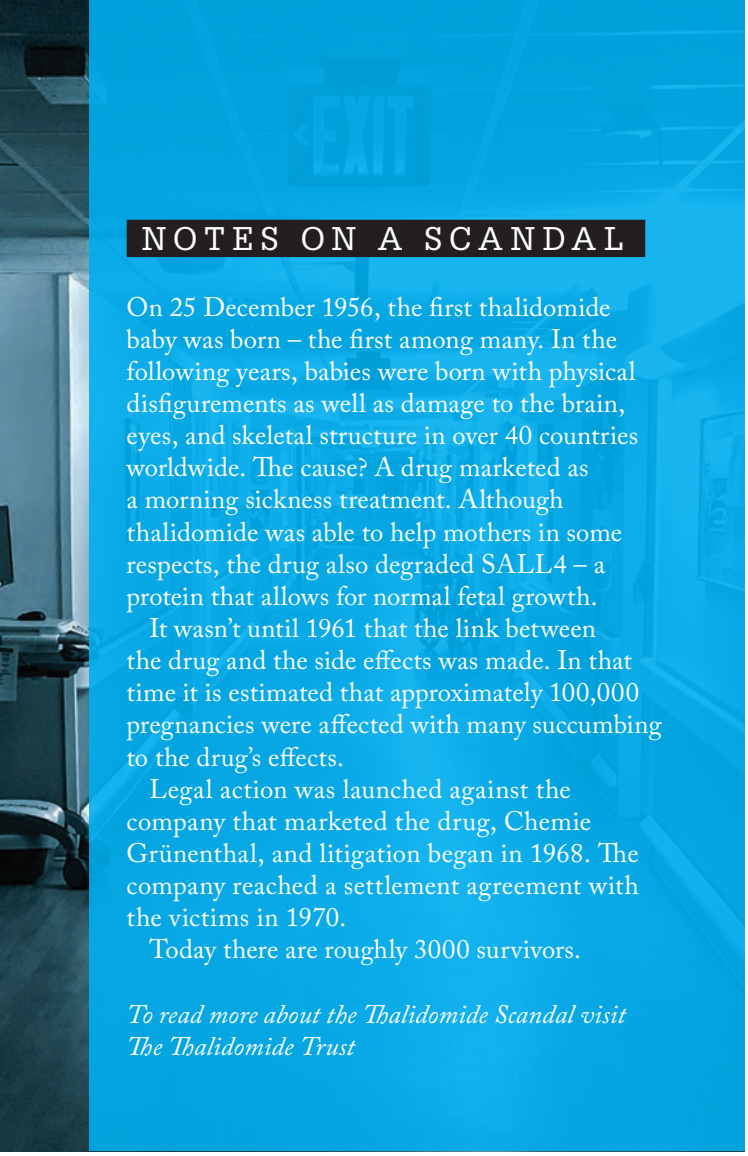
But decentralized trials aren't new. They have been around in various forms for years. It was the COVID-19 pandemic that pushed companies to further consider their benefits. Without the ability to connect face-to-face, companies had to employ digital and decentralized options to ensure the smooth running of existing trials as well as those launched during the crisis.

For Seremetis, who aimed to continue her work on clinical trials in blood disorders at Novo Nordisk during the pandemic, the move to decentralization was an unexpected but necessary step in the right direction.

Commenting on the switch to a digitalized trial approach, she says, "COVID-19 came with terrible consequences. But on a positive note, we learned that we can conduct trials remotely. It quickly became important for us to figure out how to conduct virtual conversations with patients and carry out virtual exams."

Virtual blood work wasn't a possibility, but the use of digital tools enabled the company to assess whether site visits could be minimized or locations altered to reduce travel. "Regulators also had a big part to play during his time," she says. "Though initially skeptical, they began to accept some of the new approaches that we adopted for recruiting and retaining patients." This, according to Seremetis, helped keep women engaged with trials.

But even with this positive change happening in real-time, Shangold still questions whether women of all backgrounds are aware of how they can contribute to pharmaceutical innovation. "When we expand the discussion to consider the added challenge of attracting women who are also members of other ethnic/racial minorities, we are confronted with the fact that there is frequently both a lack of awareness of clinical research study opportunities, along with much deeply-ingrained distrust of the medical/scientific community, following an admittedly-checkered past that included some infamous transgressions," he says.



NOTES ON A SCANDAL

On 25 December 1956, the first thalidomide baby was born – the first among many. In the following years, babies were born with physical disfigurements as well as damage to the brain, eyes, and skeletal structure in over 40 countries worldwide. The cause? A drug marketed as a morning sickness treatment. Although thalidomide was able to help mothers in some respects, the drug also degraded SALL4 – a protein that allows for normal fetal growth.

It wasn't until 1961 that the link between the drug and the side effects was made. In that time it is estimated that approximately 100,000 pregnancies were affected with many succumbing to the drug's effects.

Legal action was launched against the company that marketed the drug, Chemie Grünenthal, and litigation began in 1968. The company reached a settlement agreement with the victims in 1970.

Today there are roughly 3000 survivors.

To read more about the Thalidomide Scandal visit The Thalidomide Trust

From the Tuskegee syphilis trials (4) to the development of HeLa cells without the consent of the black patient who they were initially derived from (5), many communities of color have become distrustful of pharmaceutical and healthcare institutions. Overcoming this, he continues, will require continuous community outreach. "Frank and honest conversations between minority patients and their existing (hopefully trusted) caregivers are necessary," says Shangold. "Local physicians have to be involved in recruiting subjects for clinical studies, and only through consistent respect for the rights of all research participants can we, as a discipline, hope to win back the trust of these many long-disenfranchised groups."

But even if the industry is able to invest the time and effort required to mend these relationships and further employ decentralized trial platforms, there are still challenges yet to be addressed in other corners of the pharmaceutical ecosystem. The knowledge gap isn't limited to trials, and, as the industry looks ahead, it will have to expand its understanding of conditions and illnesses that exclusively and/or disproportionately affect female populations as well as the barriers that prevent innovation in the drug development process.

The future challenge

According to Shangold, funding plays a major role in the development of new therapeutics for women. Because of the complexities of the diseases that exclusively affect women – particularly gynecological or reproductive disorders, venture capitalists have become reluctant to pour investment into the companies interested in pursuing these areas of need.

"About 30 years ago, there were a handful of companies that dominated the landscape for hormone therapies – estrogens and progestins designed primarily to provide contraceptive protection or replace the natural ovarian hormones that ceased to be produced after menopause," he says. "But in 2002, when data from a large longitudinal study, the Women's Health Initiative, emerged, ideas about the safety and effectiveness of some of these drugs were upended."

Data from the study showed that some women were at an increased risk of breast cancer, stroke, and blood clots as a result of taking hormone-based medicines. The landmark results pushed physicians to reduce the rate at which these drugs were prescribed with knock-on consequences for companies' investment prospects.

Over time, some of this data was shown to be incorrect, but the damage was done. Says Shangold, "Corresponding with the change [in attitude towards hormone therapies], the availability of venture capital to fund early-stage R&D in women's health at smaller pharma and biotech companies withered as the likelihood of big pharma partnership became much less likely for some time."

Though the tide has certainly changed, the attitude that existed decades ago still has a foothold in the pharmaceutical landscape, with some companies still weary about the potential risk. However, others are actively working to make a difference. Seremetis cites the industry's attitude toward hemophilia as an example. "Two of the most prominent bleeding disorders, hemophilia A and hemophilia B, are known to be sex-linked and are generally thought of as diseases that affect men," she says. "But there are many women who are carriers of these genes who are symptomatic. Increasingly, we're thinking about them as women with hemophilia, not women carriers. This change in mindset helps us better cater to potential users of our drugs."

And although working in an entirely different area, Chris Porter, Director of the Monash Institute of Pharmaceutical Sciences (MIPS) at Monash University, Melbourne, expresses similar thoughts. Along with colleagues at US-based PureTech, he is working on developing an oral formulation of a natural neurosteroid that has been shown to treat epilepsy, depression and a range of other

neurological indications, but is currently only available as an infusion. One potential application of this medicine is in postpartum depression (PPD). Even though as many as 1 in 7 women worldwide are affected by PPD (6), treatment options remain scant. Porter says, "The only FDA-approved treatment for the disease, brexanolone (a formulation of allopregnanolone), relies on a 60-hour intravenous infusion – an obvious inconvenience to the lives of many patients. Other than this, general medicines for depression are prescribed – failing to address the distinct characteristics of the condition."

Porter and his PureTech collaborators are now developing a prodrug strategy that will enable the oral administration of allopregnanolone since the prodrug redirects the absorption process away from 'first pass' breakdown in the liver. PureTech recently announced preliminary data from a phase I clinical trial showing that this approach was able to provide oral exposure at levels approximately 9-fold higher than previous efforts to develop oral allopregnanolone. PureTech's investigational candidate is also designed to enable rapid onset of action, which would be a marked improvement over conventional depression treatments that can take weeks to have an effect. But further study is needed before any potential drugs reach patients.

These companies – and others focused on various indications – are all working to close the therapeutic gender gap. But it's clear there is still much work to be done. Aside from doing what's right – what value can businesses expect in return as they continue to make progress?

A great deal, argues Johnson. "Women are half the population and there are a number of conditions that they may experience and that require care as they mature through life. Thus, not only is women's health a therapeutic sector where innovation and fairly priced therapeutic interventions can do social good, but it's also a compelling value proposition."

References

1. *Mckinsey, "Unlocking opportunities in women's healthcare." (2022). Available at: https://mck.co/3SRfvdk.*
2. *FDA, "Guidance for Industry." (1977). Available at: https://bit.ly/3ONvd66.*
3. *"Women's health. Report of the Public Health Service Task Force on Women's Health Issues." Public health reports, 100, 73 (1985).*
4. *CDC, "The Tuskegee Timeline." (2022). Available at: https://bit.ly/3vtX83Q.*
5. *The Medicine Maker, " Remembering Henrietta." (2021). Available at: https://bit.ly/3zpNe4r.*
6. *Postpartum Depression, "Postpartum Depression Statistics." (2022). Available at: https://bit.ly/2rzmuMi.*

THE PASSION BEHIND THE PROJECT

Our experts share why women's health issues are so important to them and highlight the projects that are helping to shape the future of this industry segment

Gary Shangold, Chief Medical Officer at Enteris Biopharma

In my current role, I curate a pipeline of drugs by assessing unmet medical needs. As we all know, there is a dearth of treatments for women's health issues. Take endometriosis, for example. It occurs in 6–10 percent of US women in the general population, with approximately four per 1,000 women hospitalized each year. Uterine fibroids are another major area of concern, affecting 70 percent of women. From abnormal bleeding, pelvic pain and pressure, urinary and intestinal symptoms, and pregnancy complications, the symptoms are difficult for patients to manage. I hope to contribute to the research that will help women avoid surgery and manage pain and discomfort.

Currently, Enteris is in the process of developing an orally-bioavailable formulation of leuprolide, a widely-prescribed GnRH agonist that has been given almost exclusively as an injection. The interim data we have produced is looking good so far. If we are successful, underserved patient populations stand to gain. What could be better than offering patients a convenient and tolerable way to manage their illnesses?

Sabrina Martucci Johnson, President, Chief Executive Officer, and a member of the Board of Directors at Daré Bioscience

I founded Daré in 2015 because I saw the inexplicable and woeful lack of innovation in women's health – particularly reproductive health. I knew that we could do better as an industry. My goal is always to accelerate innovation in women's health to expand treatment options where few or none exist, enhance outcomes where current standards of care have shortcomings, and improve ease of use for women where more compelling options can drive adoption. As noted above, there are a number of persistent unmet needs in women's health – indications that are not life-threatening but are life-altering, and where, therefore, products that can improve outcomes and convenience are needed.

Because of the unique female biology, we believe that these areas of unmet needs can, in many cases, be addressed with a well-characterized active pharmaceutical ingredient (API) delivered in a different way (such as vaginal versus oral) or for indications that have not yet been addressed. By selecting a candidate (both drug and delivery vehicle) for each indication give us the opportunity to develop truly personalized treatment options for women, both in terms of their biology and overall convenience.

Stephanie Seremetis, Chief Medical Officer of Haemophilia at Novo Nordisk

Childbirth is a traumatic event. It is not uncommon for bleeding to occur. In fact, postpartum hemorrhage, which is equivalent to two units of blood loss, happens in one in every 20 pregnancies. And though the majority of these situations occur around the time of delivery, there is also the risk of peripartum and postpartum conditions that can occur 6–8 weeks after birth, causing complications for new mothers.

But if the bleeding can be stopped, most mothers can put the experience in their rearview mirror. In the case that it can't, hysterectomy or even death are real consequences. Worldwide, maternal mortality is too high; one in every 8000 pregnancies results in the death of the mother. So, what is often seen as a happy time can be a source of tragedy for many. As a consultant hematologist, one of the worst calls I would ever receive was to come to the emergency room to figure out what was happening with a young person who had just delivered a baby. If the consequences couldn't be controlled, they would be devastating. Loss of fertility and death for people who should have the rest of their lives ahead of them are terrible and harrowing scenarios…

At Novo Nordisk, we have received EMA approval for NovoSeven – a bypassing agent that is used in patients who have a factor VII deficiency. It helps to generate precursor molecules of fibrin, which is the endpoint of coagulation. It does this by upregulating several of

the steps of the coagulation cascade. But what's great about it is that it works even when this particular deficiency is absent.

By cranking up coagulation, acute bleeding episodes can be avoided. But arguably the best feature of the drug is that it is not new. It has a well-established history of use in patients with other bleeding disorders and is known to be safe and tolerable.

My call to action to the industry when it comes to women's health is to get creative. Look at the drugs that we already have on our shelves and ask how, if at all, they can be repurposed. This will only help in establishing trusting relationships between companies and the female patients they serve.

Chris Porter, Director of the Monash Institute of Pharmaceutical Sciences (MIPS) at Monash University

From the perspective of women's health, perhaps the most important project we currently have in later-stage development is an inhaled form of oxytocin for post-partum hemorrhage (PPH). Oxytocin is currently the gold-standard treatment for PPH in resource-rich countries where it is given by injection. In resource-poor settings, however, access to cold-chain storage and appropriate medical care to allow administration is a significant problem. In response, my colleague, Michelle McIntosh, and her team have developed a heat-stable form of oxytocin that does not require cold chain and can be inhaled into the lungs to allow absorption.

So, in our studies at MIPS, there are commonalities to both approaches (i.e., postpartum depression, PPD, and PPH) in that both seek to avoid the problems associated with injection. However, tailored approaches and solutions to each are required. In the case of PPD we have developed an oral prodrug formulation, and for oxytocin in PPH we are exploring pulmonary administration.

RIGHTS, DENIED

Women's rights are human rights. Though this may seem like a statement of the obvious, events of recent months have proven that the voices of women can be overshadowed and overlooked even when the decisions being made affect their lives and wellbeing. The overturning of Roe v. Wade by the US Supreme Court marked a new – and worrying – turn in American history. Women across the nation are now at the mercy of the state they live in when it comes to their abortion rights. Several states have codified abortion restrictions into law – preventing women from receiving what used to be an easily accessible healthcare treatment.

The ruling sets a negative precedent. Although there have always been barriers to abortion in some parts of the world (it is limited or completely restricted in several countries), some are concerned that the USA's decision could stir change in places where the service is currently available. Conversations about how the US ruling will affect healthcare standards have now come to the fore. At the time of writing, the UK is in a diplomatic skirmish with EU countries over its removal of guidance on abortion from a statement on gender equality.

But as discussions intensify, how will the pharmaceutical industry respond? Drug-making companies have an integral role to play – providing the drugs that can help initiate or accelerate abortion. Now more than ever before, the industry is focused on health equity.

As women across America are increasingly stripped of this fundamental right, companies will have to consider how they can continue to support equal and fair medicines access and treatment for all. Here, Lisa Maldonado, Executive Director of the Reproductive Health Access Project, shares her views on the landmark ruling and predicts what the industry's future relationship with female patients will look like.

What concerns you most about the Supreme Court's decision to overturn Roe v. Wade?

With this ruling, the Supreme Court of the United States has dealt a massive blow to abortion access for millions of people across the country, and put many other civil liberties at immediate risk, including marriage equality, access to contraception, the right to privacy, religious freedom, and more. The decision is not just an attack on our reproductive rights – this is a full-scale assault on our right to determine how we live our lives.

What consequences will the decision have for pharmaceutical companies and distributors?

It seems to me that the most pressing concern at the moment would be for the pharmaceutical companies that make mifepristone – one of the abortion pills available in the US. As states are now fully empowered to regulate abortion, the impact will differ state by state. However, the Attorney General of the United States did issue a statement that said states may not ban mifepristone based on disagreement with the FDA's expert judgment about its safety and efficacy.

"This ruling [...] has dealt a massive blow to abortion access for millions of people across the country."

Could the decision impact the use of certain types of contraception like Plan B?

Plan B is not an abortifacient, it does not end a pregnancy, rather it prevents pregnancy. So, like all other contraception, it should not be affected by the Supreme Court's decision in the Jackson case. If states do try to limit access to contraception as a result of the Supreme Court decision, pharmaceutical companies and others need to push back swiftly and strongly.

Online searches for abortion pills have surged in the wake of the recent decision. How, if at all, will the ruling affect the counterfeit and falsified drug product market in the US?

People have been obtaining abortion pills online safely for quite some time. Helping people who are self-managing their abortion to avoid counterfeit and falsified products will be important. Groups like Plan C provide up-to-date information on how people in the US are accessing at-home abortion pill options online.

What should pharma companies pay attention to as this issue continues to unfold?

They should monitor unnecessary restrictions and regulations on FDA-approved medications, including contraception and abortion pills. Pharma companies can also work to make contraception available over the counter, thereby expanding access.

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Mastering mRNA Manufacturing

Top tips from two industry experts

mRNA is revolutionary – and it's most probably here to stay. We speak with two experts from Sartorius – Integrated Solutions Manager Ganesh Kumar (GK) and Global mRNA Process Technology Manager Nargisse El Hajjami (NEH) – to ask their advice on the next generation processes and facilities that can help you master mRNA manufacture.

What are the biggest trends in mRNA manufacturing?

NEH: One could argue that mRNA manufacturing is, in itself, a trend! During the pandemic, our society witnessed just how effective, fast, and flexible an mRNA platform could be for vaccine production for an infectious disease. More and more biopharma customers now want their own mRNA manufacturing capacities, although the specific trends vary depending on what modalities and applications customers are pursuing. Without a doubt, many challenges remain in optimizing nucleic acid constructs, delivery systems, manufacturing processes, stability, and efficiency for mRNA products, and we see a big focus on applying innovation at different levels to support the rapid growth of the field.

One of the largest missing puzzle pieces today is a standard process template or platform for producing mRNA. The field is still in its infancy and we still don't have that much data around existing technologies' performance, process parameters, and yield control. In addition to this, the existing variability in mRNA constructs with various sizes and properties leads to variability in process performance and steps, which makes the standardization of a platform even more complicated.

We are also still missing stable and efficient solutions for mRNA delivery because currently there are still challenges in handling formulated nanoparticles at very low temperatures and assuring efficient delivery of mRNA into specific sites of the body. In this area too, we see a lot of work exploring innovative encapsulation methods and next generation delivery systems to assure safe and effective mRNA delivery to targeted sites.

Process design is another key challenge. There is an entire intellectual property landscape growing around process steps and the technologies used. A process can be the strength of a company, because with the same template you can potentially produce any mRNA sequence to produce any protein target and trigger different applications using the same process flow with minor process adaptation, and by simply changing the sequence content of your DNA templates.

GK: We are also seeing efforts to simplify facility design and reduce running costs by – to give a few examples – creating fully closed processes with an optimized single use (SU) setup, modular systems in a ballroom concept, and implementing in/at-line process analytical technologies for the measurement of critical process parameters (CPPs) and data analytics for prescriptive control.

In time, we may see the industry segment itself into a set of manufacturing platforms specialized for different varieties of mRNA constructs, different scales of production, and so on.

Why is the variability of mRNA design such an issue?

GK: First-generation mRNA processes were typically linear and used traditional mRNA, but there are numerous other types of viable constructs that are being explored, such as self-amplifying and trans-amplifying RNA, which could have a positive impact on cost of goods, drive process miniaturization, and require less doses (almost or greater than a log reduction in some cases) to treat patients.

NEH: The issue with variability is multi-levelled. First, we could be talking about mRNA variability in terms of sequence construct or type as mentioned previously. Specifying the type of mRNA – for example modified, self-amplifying, non-replicating, or circular – is important because different sizes, forms, and properties of mRNA demand the adaptation of process steps and used technologies. It's not only the efficient purification of large size mRNAs that can be difficult – sterile filtration can also be near-impossible. One would need to set up alternative solutions, assure sterility, and meet the relevant regulatory requirements. Second, we could be talking about mRNA variability in terms of DNA template origin – for instance DNA template from E. coli compared to synthetic DNA – because different origins will produce different levels of contaminants. All of this can impact process design, potentially adding more steps to setup. More process steps will demand more space, more testing and validation, and inflict higher costs. The lesson here is that choosing the right strategy for mRNA with the end in mind is crucial. The fact that so many options are now in play only underlines this.

What considerations should factor into the design of new mRNA facilities?

NEH: The manufacturing process should be at the core of the facility design. You must ensure that you are implementing a process flow that is robust, efficient, fast, and cost-efficient – and that your facility is designed to support this process while allowing enough flexibility to quickly and easily adapt to changes and growth.

It is important to consider innovative technologies and next generation solutions for the different aspects of mRNA manufacturing while designing your mRNA facility, all to better support the need for speed.

GK: Some of the key questions that must be considered are scale, single product versus multi-product, current titres versus future state titres, localized versus centralized manufacturing, and in-house versus outsourced pDNA manufacture.

Though RNA-based modalities are relatively new, biopharmaceutical

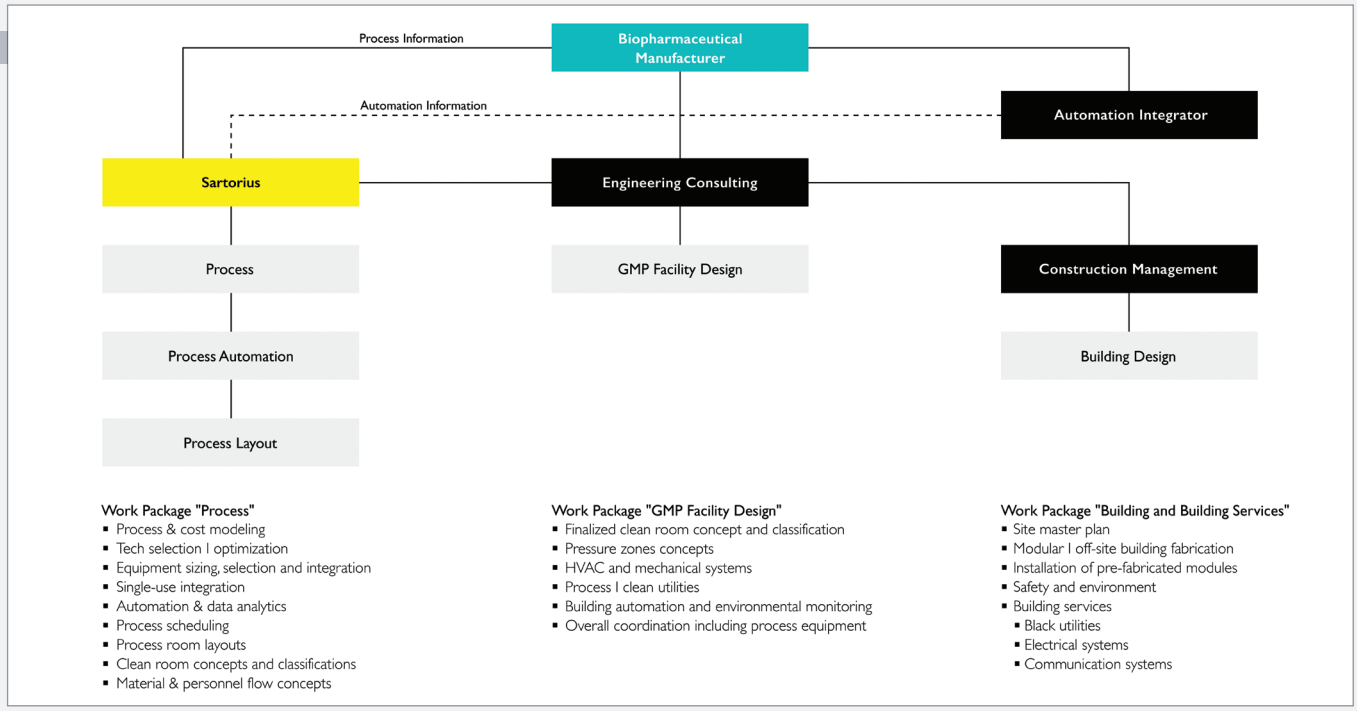

Figure 1: Sartorius Conceptual Design Setup for a state-of-the art SU facility

manufacturers can rely on the available standardized industry approaches and tools to help get started. For example, at Sartorius, we have a standardized conceptual design package that has been successfully applied in process and facility design for mRNA manufacturing. As outlined in Figure 1, we actively work with our customers to first model, optimize, and define the process with the associated technologies. After this, the equipment, SU concept, scheduling, automation strategy, and preliminary process layouts with personnel/material flows can be generated based on the process and its risk assessment (1). Through active collaboration the biopharmaceutical manufacturer, engineering, consulting, and construction companies, the outputs from the process package can be successfully incorporated into the GMP facility design and building packages to rapidly build the SU facility with modular/prefabricated clean rooms, as required.

With such approaches, we successfully partner with biopharmaceutical developers across the globe to share our expertise and help them accelerate the design and implementation of their manufacturing strategy/facility.

NEH: To summarize, it is crucial to select the right manufacturing strategy and supply partners that can support you at different levels. You'll need the right expertise and experts to help develop your process, optimize your manufacturing, design your facility, and select suppliers that will help you accelerate your journey.

How does Sartorius support mRNA developers?

GK: We offer customers solutions across upstream and downstream workflows for the manufacture of plasmid DNA.

For *in vitro* transcription and mRNA purification, we have a scalable bioreactor portfolio that offers a high degree of monitoring and control, as well as a scalable downstream toolbox based on convective monolithic chromatography media and flat-sheets/hollow-fibers for TFF applications. These allow us to accommodate different mRNA constructs using a platform purification approach.

Last but not least, we also offer services related to development and optimization of the process development and manufacturing workflows. For example, we work with our manufacturers to logically develop and optimize pDNA or mRNA purification platforms through Cornerstone Process Solutions. When dealing specifically with manufacturing workflow, we have conceptual design (as previously discussed) and value chain services that help our customers choose the right process, technology, Facility design, SU, and automation strategy to help them move towards a 'smart' modular facility.

NEH: mRNA storage and shipping are important aspects of mRNA manufacturing that require specific attention given the instability and sensitivity of mRNA products to handling, shear, and temperature upon lipo nano particle (LNP) formulation. For formulation and storage, we provide solutions covering development from the lab to large-scale manufacuring. On one hand, we provide a formulation and filling process development mRNA package to support mRNA developers on screening and identifying CPPs and critical quality attributes, and setting up their design space. They can then speed up their LNP development with a high throughput screening, tangential flow filtration, and controlled freeze/thaw system (2). On the other hand, we also offer a late-stage storage and shipping mRNA package that helps ensure stability during LNP storage and shipment, with a fully scalable freeze/thaw system and adapted storage solutions.

References

1. *Sartorius, "Bioprocess Consulting & Engineering" (Sartorius, 2022). Available at https://bit.ly/3pMmsPi*
2. *Sartorius, "Lab-Scale Benchtop Freezing" (Sartorius, 2022). Available at: https://bit.ly/sr-freeze*

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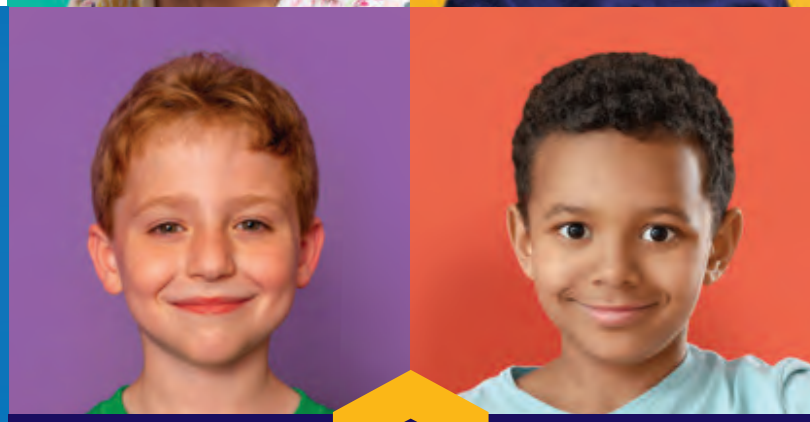

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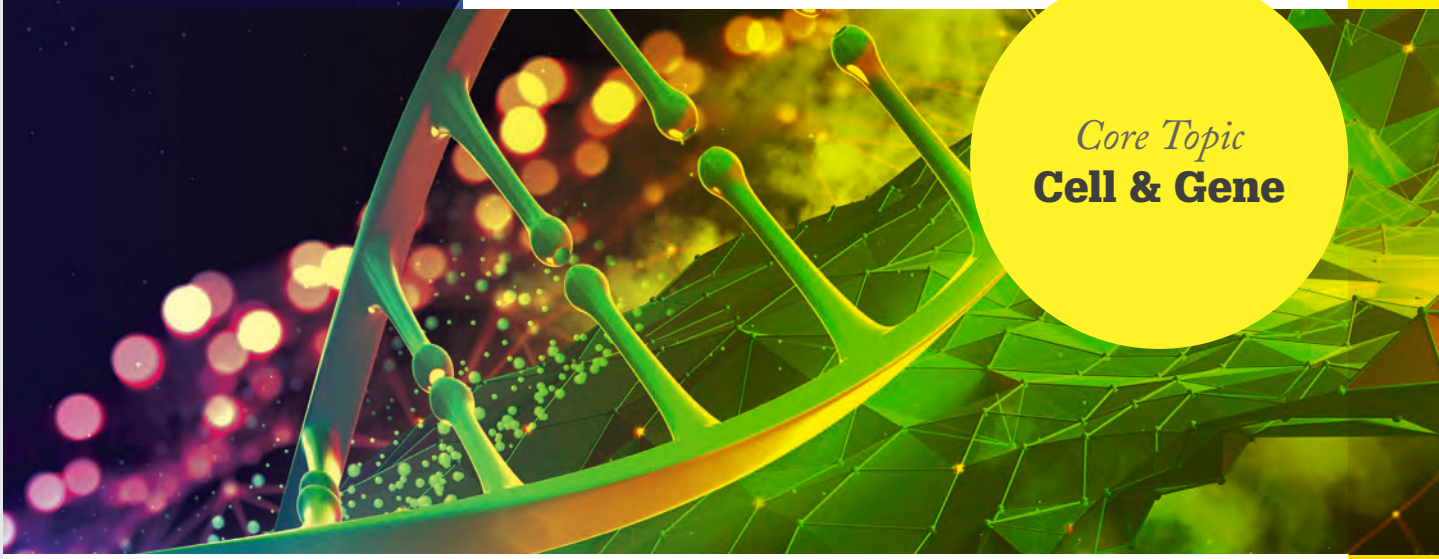


Core Topic
Cell & Gene

Gene therapy for HIV. Once, HIV was the scariest disease in the world. By 2008, the number of children orphaned by AIDS deaths was 19.6 million and still rising. But new therapies have emerged and more are on the way, including a one-off gene therapy set to enter preclinical studies. The research will be led by Jonah Sacha of Oregon Health & Science University, and will be funded by a grant worth up to $5 million from the NIH's National Institute of Allergy and Infectious Disease. The treatment is a gene therapy adaptation of leronmab, a monoclonal antibody that Sacha found could prevent HIV infection in monkeys.

The nameless newborn. In 2021, ElevateBio and Boston Children's Hospital announced that they had teamed up for a five-year cell and gene therapy collaboration that would – among other things – allow them to form companies together. The agreement has now borne fruit. The two have birthed a new (but as-yet-unnamed) spinoff company that will "develop allogeneic immune cell therapies based on a novel platform that generates functionally mature immune cells from induced pluripotent stem cells." The platform comes backed by a paper (DOI: 10.1016/j.stem.2022.06.014) published in Cell Stem Cell, that details a novel differentiation process devised in George Daley's lab at Boston Children's Hospital.

And the blind shall see… It's a somewhat biblical promise. But advanced therapy does deal in cures – and a cure for blinding retinal disorders is exactly what a team across several Philadelphia institutions (led by the University of Pennsylvania School of Veterinary Medicine) is working towards. In a newly published study, the team demonstrated significant progress toward a therapy that would reintroduce healthy dish-grown photoreceptor cells to the retina, overcoming serious technical roadblocks in cell mortality and integration for regenerative therapy. To inject these cells, the team developed a new surgical approach in collaboration with UPenn's Bharti Lab.

Deaths on the label. Media outlets are reporting the deaths of two patients (one in Russia, one in Kazakhstan) from acute liver failure after being treated with Zolgensma, Novartis' gene therapy for spinal muscular atrophy. Serious liver issues are a known side effect of the drug – they are the reason it comes with a black box warning – but these appear to be the first deaths triggered by the treatment. Novartis has reportedly asked regulators to update the labeling to state that serious liver failures resulting in death have been reported. The company also stated its continuing confidence in the treatment's risk/benefit profile.

IN OTHER NEWS

CureHeart wins British Heart Foundation's Big Beat Challenge, receiving £30 million to develop injectable cure for inherited heart muscle conditions

In study profiling molecular features of T cells, Children's Hospital of Pittsburgh scientists discover that even the most worn out T cells retain some function that could be "brought back" for further action as cancer immunotherapy

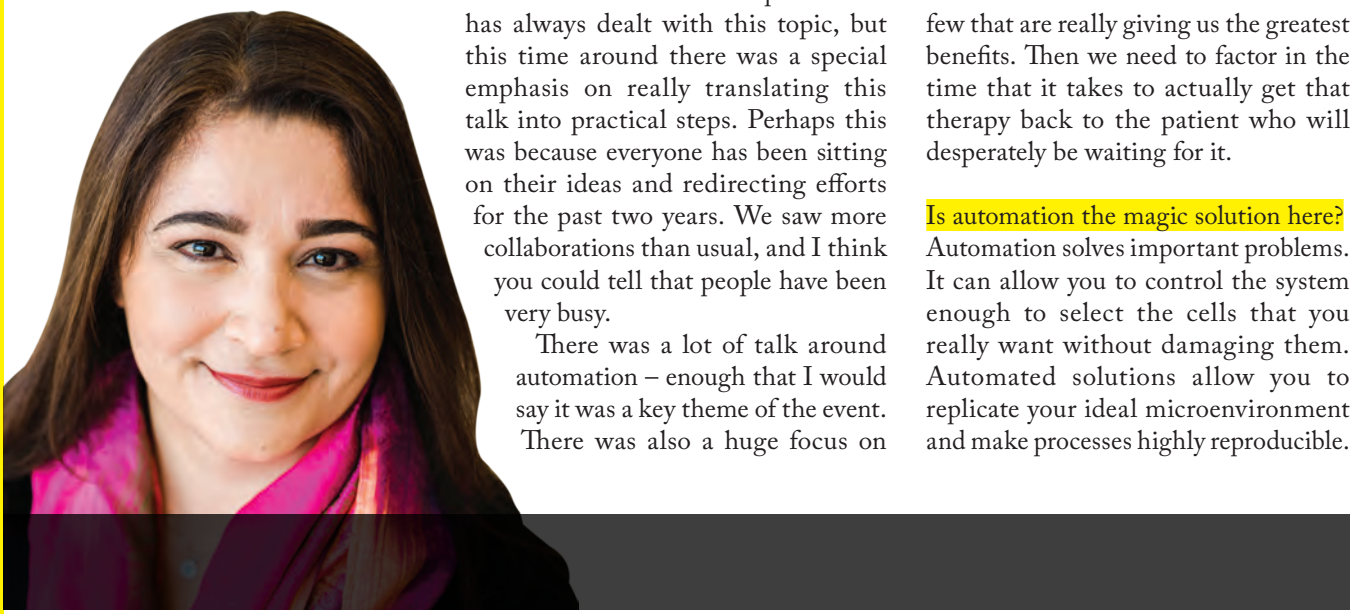
Roche offers up to $1 billion to Pittsburgh Medical Center spinout Avista Therapeutics for rights to adeno-associated virus engineering platform technology, scAAVengr, to help commercialize gene therapies for rare ophthalmic conditions

Prompted by reports of clinical improvements in lupus patients after stem cell infusions in a single center in China, phase I lupus trial in US finds stem cell therapy lessened effects of disease in five of six participating women; larger phase II trial looks set to go ahead

ISCT 2022: Post-Conference Reflections

The International Society for Cell & Gene Therapy convened in person for the first time in two years. Here, we learn how it felt, what was said, and what comes next.

Absence makes the heart grow fonder. You don't know what you've got until it's gone. Both cliches, but both proven very true by COVID-19. Delara Motlagh, General Manager for Cell Therapy Technologies at Terumo Blood and Cell Technologies, would likely agree that, though meeting and working online has incredible upsides, it simply cannot capture the magic of a real-world meetup. Here, we speak to Motlagh about her experience returning as an in-person attendee to the International Society for Cell & Gene Therapy (ISCT) annual meeting for 2022.



In one sentence, how would you describe ISCT 2022?

Fundamentally, it was a forum where folks shared their news on advancements in the industry and discussed the challenges facing cell and gene therapy – with a focus on commercializing the therapies and figuring out how we can treat more patients.

And was it a success?

It was a huge success! The organizers took a risk in planning the conference as an in-person event, but the turnout was great and everyone was delighted to be together once again. It really augmented the learning and the sharing.

Having gone through two consecutive years of virtual communication, we were able to appreciate how much more you can get done in person – in everything from intricate networking to the simple act of shaking hands. There's just no virtual substitute for it.

Aside from the shock and joy, what was new this year?

This year, we saw a particular focus on all the different elements that we need to commercialize our therapies. ISCT has always dealt with this topic, but this time around there was a special emphasis on really translating this talk into practical steps. Perhaps this was because everyone has been sitting on their ideas and redirecting efforts for the past two years. We saw more collaborations than usual, and I think you could tell that people have been very busy.

There was a lot of talk around automation – enough that I would say it was a key theme of the event. There was also a huge focus on the quality versus quantity of the cells that we use, which then naturally feeds into questions regarding the tools that developers will use. It was all about asking how we use the various innovations in the field to support the broader ecosystem for developing and manufacturing advanced therapies at scale.

In quality versus quantity, do you have to make some hard tradeoff decisions?

Yes, there are tradeoffs. For example, suppose you're trying to grow a cell. A cell is a living thing, and just like you and I, it gets tired. So if we're trying to reproduce a huge number of copies of that cell, it will eventually become exhausted. A cell that's exhausted might not be as beneficial when you try to use it for therapy. The next factor to consider is the duration. If your company is trying to rack up one billion cells, it will fall a few days behind the company shooting for one million cells. The final product will look different, too.

So, to manage the tradeoff here we have to take care of those cells and make sure that we don't exhaust them, and then we need to select the critical few that are really giving us the greatest benefits. Then we need to factor in the time that it takes to actually get that therapy back to the patient who will desperately be waiting for it.

Is automation the magic solution here?

Automation solves important problems. It can allow you to control the system enough to select the cells that you really want without damaging them. Automated solutions allow you to replicate your ideal microenvironment and make processes highly reproducible.

All of this speeds up and standardizes the number of days needed to get that product out. It de-risks the process. Remember that a simple mistake at any point can prevent the therapy reaching the patient, so mitigating risks is crucial.

What were some of the most interesting conversations you had at ISCT?

There were many interesting discussions! For me, some of the most engaging among those were the conversations that turned to companies such as Novartis, whose goal is to begin with a process that can run for up to two weeks, and condense it down to just a few days.

Conversations around process testing were key here; if the testing process eats up one week then it does you no favors. Testing and validating the various parameters in the process upfront is the answer.

Another pain point we explored is the moment of collection. For all the intricacy that follows, the entire process begins with a single drop of blood. Here, standardization is the panacea. The industry is crying out for it. Standardizing the incoming product wouldn't just benefit companies and their material-hungry pipelines – it would also ensure a better experience for patients and donors.

What changes are you expecting to see in the short, medium, and long term?

Ultimately we're all here because we want to save lives, and I think the biggest hope for the industry is exactly that. These life-saving drugs have the potential to become the standard of care. The question is, how do we make that happen?

If you look at the ecosystem in cell and gene therapy today, you'll see it's already quite strained. We have only a limited number of centers able to deliver these therapies and every company in play is racing to accelerate their products' pathway to the market.

The problem of "access" very often boils down to the hard problem of "cost," and rightly so, because these are expensive therapies. Yet, if we analyze the cost, we see that it's not the therapy itself that's so expensive – it's all of the different elements that go into delivering it to the patient.

You can read more from Delara Motlagh at www.themedicinemaker.com

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Core Topic
Bioprocessing

Monkeypox concerns. WHO has declared the monkeypox outbreak a "public health emergency of international concern." More than 41,000 cases have been reported across the world, as of mid-August, including 12 deaths, but a smallpox vaccine is helping. The European Commission has extended the marketing authorization for Bavarian Nordic's smallpox vaccine, Imvanex, to include protection from monkeypox and disease caused by vaccinia virus. The FDA has issued emergency use authorization for the same vaccine (under the name JYNNEOS) for use in the US for those at high risk of infection. Bavarian Nordic has recently entered into vaccine contracts with multiple governments.

Advancing the field. The National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL) has announced $15.8 million funding for 14 biopharma manufacturing projects. Projects include scalable technologies for cell therapies, an integrated continuous USP platform, virus and endotoxin clearance strategies, bioprocessing sensors for online monitoring, clearance and quantification of host cell proteins in mAbs, as well as a handful of projects dedicated to training the workforce and promoting biopharma manufacturing careers to high school students. More details about the projects are available on NIIMBL's website.

On the way out. Demand for COVID-19 vaccines in the western world is decreasing – which means vaccine revenues and profits are dropping too. BioNTech has announced Q2 revenues of around $3.3 billion, down from $5.4 billion for the same quarter in 2021. However, overall revenues from the company's COVID-19 vaccine are still expected to be in the region of $13-17 billion for the full year. Things aren't looking so rosy for Novavax, which halved its revenue forecast in August from $4-5 billion to $2-2.3 billion.

Targeting viral vectors. Researchers from the University of Arkansas, University of Kentucky and Clemson University have received a $6-million grant from the National Science Foundation to develop purification membranes suitable for large-scale manufacture of viral vectors and virus-like particles. The goal is to replace the standard processes of centrifugation and resin-based chromatography, which are both difficult to scale up. The research team will be designing, fabricating, and characterizing high-capacity membranes, as well as developing membrane chromatography for separating full and empty viral capsids.

IN OTHER NEWS

FDA approves AstraZeneca and Daiichi Sankyo's HER2-directed antibody drug conjugate Enhertu (trastuzumab deruxtecan)

Pfizer and Valneva initiate phase III trial of Lyme disease multivalent protein subunit vaccine VLA15 involving 6000 participants

BioNTech and Genmab expand ongoing oncology collaboration to include R&D and commercialization for novel monospecific antibody candidates

UK's MHRA conditionally approves Moderna's bivalent COVID-19 booster, which contains Spikevax and vaccine candidate targeting the Omicron variant

NIAID awards $6.9 million to Institute for Bioscience and Biotechnology Research to design a vaccine against hepatitis C

Medicine Makers of History: Salk and Sabin

In this new regular column, we'll be taking a look at important medicine making moments throughout history. First up – here's how two rival vaccine projects shaped the modern disease landscape for polio

By Angus Stewart

Jonas Salk at Copenhagen Airport, 1959

Credit: SAS Scandinavian Airlines

Polio has returned to the United States of America. In New York state's Rockland County, one person tested positive for the disease on July 21, 2022. Two weeks and one day later, the polio virus was found in samples of New York City wastewater.

Meanwhile, in the UK, a striking headline broke on August 10: "All children aged 1 to 9 in London to be offered a dose of polio vaccine." The decision came from the UK's Health Security Agency, and was in response to a slew of detections of polio in London wastewater. As in New York, these traces are most likely derived from individuals who had recently received oral polio vaccines (OPVs), which use a live version of the virus that has been shown to cause one case of disease per 2.64 million doses.

A great thinker once said history repeats itself first as tragedy, then as farce. In the potential (and completely avoidable) return of a once-terrifying disease to the ever-blacker comedy of the 2020s, we can see this idea in motion. So perhaps now is a good moment to look back in time to the origins of the two unpatented polio vaccines.

The story leads us back to two US scientists, Jonas Salk and Albert Sabin. Salk is the man behind the prestigious Salk Institute, and also the inactivated polio vaccine (IPV). Sabin, his rival, created the oral polio vaccine (OPV). Roughly of an age, both men got their start in academic lab work in the interwar years. World War II saw them both briefly work on medicines for the US army, and the peacetime that followed saw them each commit to creating a polio vaccine.

Sabin's interest in poliovirus began before the war, so at war's end he merely picked it up again. Salk, on the other hand, was recruited by the March of Dimes, a charitable foundation set up by the country's most famous polio patient – President Franklin D Roosevelt. This difference is crucial since the March was able to mobilize mass public awareness and a flood of small donations from ordinary Americans that put the spotlight on Salk's work, and funded it right to the finish line with little need for state support or corporate revenue. Perhaps enabled by this bottom-up funding model, Salk famously declined to patent his vaccine. When asked why on live television, he answered: "Who owns this patent? Well, the people, I would say. There is no patent. Could you patent the sun?"

Following successful trials, the rollout of Salk's vaccine began in peachy fashion. Despite an initial hiccup regarding stocks and supplies, the vaccine rolled out to immunize children across the country. It also traveled overseas to US allies in Western Europe.

But the tables soon turned. Effectively blocked in the US by Salk's success, Sabin took up an offer for the USSR. Working with virologist Mikhail Chumakov, he helped the Soviet Union to develop and test his vaccine, then roll it out. Sabin's OPV became even more international than Salk's IPV, with immunizations being carried not only in Russia and the other territories of the USSR, but also in Warsaw Pact countries like Hungary and East Germany, and further afield in nonaligned countries like Mexico. In 1962, Cuba took on Sabin's vaccine and used it to bring polio down from annual numbers in the hundreds to a total of 10 confirmed cases between 1963 and 1989.

Doubts around the Salk vaccine's superiority grew, fuelled in part by the infamous "Cutter Incident" error that saw tens of thousands of children infected, 56 paralyzed, and five dead, with an additional 113 adults paralyzed and another five killed. Eventually it was the Sabin vaccine that became the global standard, driving a vast pushwar push that came close to totally eliminating polio globally.

In the US the oral vaccine was served to schoolchildren on a sugarcube, which indirectly inspired the Sherman brothers' A Spoonful of Sugar (Helps the Medicine Go Down). This poses an intriguing philosophical question about whose social/cultural legacy is most significant: Salk for setting up his Institute, or Sabin for inadvertently granting Mary Poppins her most famous song?

In the end the Salk vaccine took back the throne, and holds it to this day. This is because Sabin's active vaccine causes one case of the disease per 2.64 million doses, and thus has become one the final barriers to totally eradicating polio. Should a post-polio world ever be achieved, both vaccines will have created that world, but it will need to be Salk's alone that maintains it.

Embracing the Digital Transformation

How does digital transformation create a competitive advantage for customers and emphasize Bachem's technical leadership role in the TIDES CDMO field?

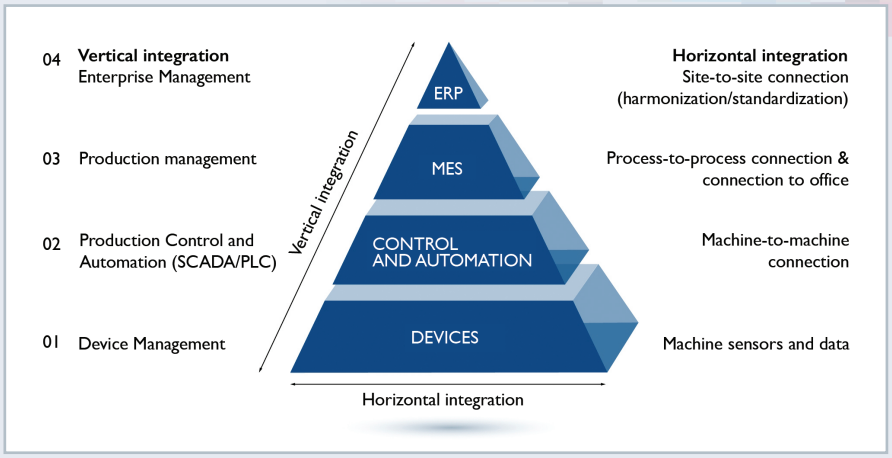

Figure 1. The automation pyramid for state-of-the-art manufacturing of peptides and oligonucleotides (TIDES)

The fourth industrial revolution has started slowly in the pharma and biotech sectors, but more and more companies now embrace digital transformation in operations and supply chains (1). At the beginning, the drivers for digital innovation were cost savings and productivity, but there are many business cases beyond financial KPIs. For example, improved flexibility in capacity allocation and production scheduling can shorten time to market for new modalities, such as oligonucleotides. Oligonucleotides are a growing sector of the market, with 15 products already approved and more than 900 products in preclinical and clinical trials. Both the market and demand continue to grow, and digital transformation represents a great opportunity for CDMOs to keep pace with the dynamic landscape.

As the technology-leading CDMO for peptides and oligonucleotides, Bachem sees digitalization as an enabler to meet changeable demands, compliance, and ambitious timelines for high-quality APIs. Taking the automation pyramid (see figure 1) as a framework, digitalization projects are required in all layers in the digital transformation journey of pharmaceutical operations towards Industry 4.0.

One of our recent digital transformation lighthouse projects was the full automation of the industrial solid phase peptide synthesis (SPPS) process. To this end, the first Bachem robot-operator was designed and programed to execute the complete amino-acid activation and addition step. A key component of the automated equipment train is process analytical technology (PAT), which enables inline monitoring after key steps. With PAT, the need for manual in-process controls is omitted while ensuring real-time control of critical process parameters.

In addition to full automation, we digitalized our SPPS process by integrating the control system of the production floor (levels 1 and 2; see figure 1) with a manufacturing execution system (MES, level 3), and the enterprise resource planning (ERP) system (level 4).

The MES has three major tasks:

- lead the process control system by defining the sequence of operations that have to be performed: Master Batch Record
- record all events, process values, and alarms as they happen during the process, and generate the electronic batch record
- manage equipment status (point-of-use and status verification, calibration, cleaning recipes etc) with integrated digital logbooks

In the context of vertical integration, the MES interconnects with our ERP system. Material verification, execution of process orders, creation of manufacturing orders, automatic stock creation, and material flow are all tasks that are now fully automated and paper-free. The risk of human error, such as material loss or mix-up, is omitted. The process means that we can ensure that the correct material is used at the correct process step, as well as a reliable stock and inventory management generating a single source of truth in the ERP system.

All process data is logged in real time in the plant information (PI) system, which is a data Historian platform. This platform enables long-term archiving of process data, batch data, and facilitates data analytics, process optimizations, or root cause investigations. Both MES and PI systems are being rolled-out company wide.

Entering the era of pharma 4.0 demonstrates our commitment to our customers. Bachem has made huge steps in ensuring swifter interaction, more flexible production, and documentation sharing. With these newly integrated systems, we increase our capacity and speed by streamlining GMP documentation while boosting our processes' efficiency regarding quality, cost, and time. Digital transformation will allow us to meet the increasing demand for new modalities and increase the speed with which these new therapies can reach the market. Thus, we will help our customers in their mission to reach large patient populations and to transform as many lives as possible.

CDMO: Contract Development and Manufacturing Organization

Reference

1. G Hole et al., International Journal of Pharmaceutics: X, 3 (2021). DOI: 10.1016/j.ijpx.2021.100095

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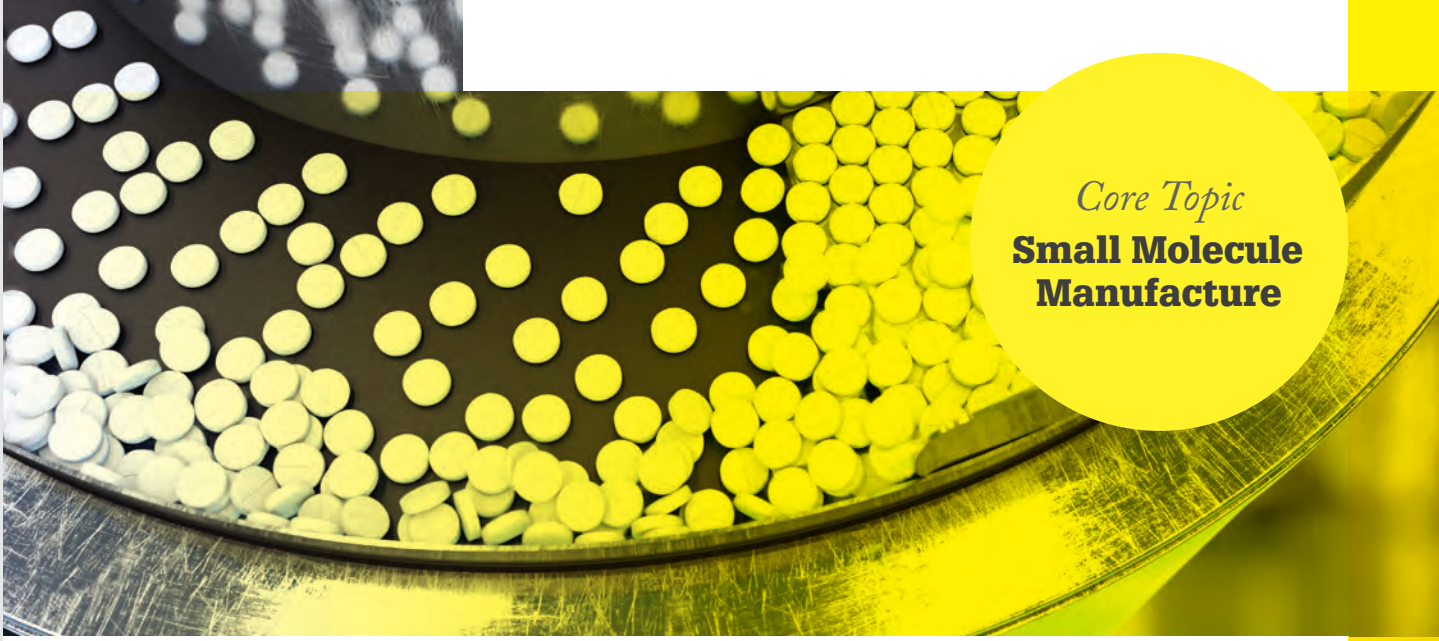

Core Topic

Small Molecule Manufacture

Under review. The EMA's Emergency Task Force has launched a review to assess whether a drug, sabizabulin, has the potential to treat COVID-19. Manufactured by the pharma company, Veru, it is thought to be able to reduce inflammatory reactions associated with the disease. Though the company hasn't yet applied for marketing authorization, the EMA has decided that – results permitting – the drug could be used in its member states beforehand. The review will rely on data garnered from hospitalized patients with moderate to severe infection who are at risk of acute respiratory distress syndrome and death.

UK critical shortages. A survey published by The Pharmaceutical Journal reveals that 54 percent of UK pharmacists believe that medicine shortages within the last 6 months have put patients at risk. The availability of common OTC drugs, including painkillers and condition-specific treatments such as hormone replacement therapies, has dwindled with many pharmacies struggling to meet patient needs. The British drug pricing committee, the Pharmaceutical Services Negotiating Committee, claims that pharmacies nationwide face "a critical situation trying to source medicines in [a] timely manner."

Preventing preterm problems. Preterm birth is a leading cause of death worldwide. Though several approaches are used in attempts to prevent it, some are skeptical about the use of pharmaceuticals. Historically, the tocolytic drugs used are questionable with respect to their safety and tolerability. But now a collaborative research effort launched by the WHO and the UK's University of Birmingham has shown that they are safe, with their benefits outweighing any potential risks. In a meta-analysis of over 120 trials, the team found that the vast majority of drugs studied (which included betamimetics, calcium channel blockers, magnesium sulfate, oxytocin receptor antagonists, and nitric oxide donors) were well-tolerated and safe.

An unexpected ingredient. US-based supplement manufacturer, Sangter, has voluntarily recalled its 12-blister pack 300 mg energy supplement for failing to declare that the product contained sildenafil. Sildenafil is the active ingredient in Viagra. The FDA claims that the supplement could potentially pose harm to human health because it could interact with "nitrates found in some prescription drugs (such as nitroglycerin) and may cause a significant drop in blood pressure that may be life-threatening."

IN OTHER NEWS

Drug candidate, fabimycin, shown to have broad antimicrobial potential – with potency proven against 300 drug-resistant bacterial strains

Due to genetic variation among patient populations, psychedelic drugs including psilocin and LSD behave differently at serotonin receptors

Nanoparticle technology designed by Washington University researchers is capable of preventing blood vessel rupture

PhRMA joins clinical trials diversity initiative, Equitable Breakthroughs in Medicine Development, alongside other industry and academia groups

Research shows that body posture affects absorption of oral drugs with pill movement and dissolution rate dependent on positing of GI tract

The Candy Coder

How can data be stored in candy? And how could it be used to fight counterfeit medicine?

By Stephanie Sutton

Did you see the fascinating and visually vibrant work of William Grover in the media over the summer? Grover – a bioengineering professor at the University of California Riverside – covered pills in candy sprinkles and demonstrated how the approach could work as an anticounterfeiting measure (1). Sounds bizarre, but, as Grover points out, counterfeit medicines are still a global problem despite all the effort the pharma industry has put into this area. We need more solutions.

Here, we learn more about CandyCode.

Why is the authenticity of pharmaceuticals such an interesting topic for you?

Fraudulent pharmaceuticals are fascinating because they're just downright evil. Imagine making pills out of plaster and selling them as antimalarials for sick children... I'd do anything in my power to fight that.

I hope that the tools and techniques my lab has developed can make a real difference in the fight against counterfeit pharmaceuticals. But even if they don't, I'm still grateful I've had the opportunity to draw attention to this problem.

What inspired your work with CandyCode?

It honestly started one day when I was eating some little chocolate candies that are covered with multicolored sprinkles called "nonpareils." I noticed that the nonpareils are applied to chocolates at random, which made me wonder if the patterns ever repeat themselves. After studying a bunch of candies and doing some math, I discovered that the nonpareil patterns are indeed unique and unlikely to ever be repeated by chance – even if you made astronomically large numbers of candies – and that means the patterns could be used as "universally unique identifiers."

Since they are unique, easy to produce, and hard to counterfeit, I realized that these "CandyCodes" could be applied to pills and capsules to combat pharmaceutical fraud. By coating each pill with nonpareils and then taking a photo of each pill before it leaves the production facility, a pharmaceutical company could create a database of known-authentic pills based on their CandyCodes. Then, when a consumer wishes to confirm the authenticity of their CandyCoded pill, they can use a smartphone camera to snap a photo of the pill. If a matching CandyCode is found in the manufacturer's database, then the pill is authentic, but if no matching CandyCode is found, the consumer would be warned that the pill may be counterfeit and should not be consumed.

What are the main benefits of this approach?

I believe that CandyCodes are the simplest and most feasible way to put unique identifiers directly onto a pill or other drug product.

Other researchers have proposed various on-drug IDs to combat fraud, but their implementations haven't seen widespread adoption because they require significant alterations to the drug formulation or manufacturing

process, or they require consumers to have specialized equipment to read the IDs.

CandyCodes are just particles applied at random to a pill or capsule. They require no alteration of the drug formulation and only minimal alteration of the manufacturing process – basically just adhering edible colored particles to each pill and then photographing them. They're easy to make but very difficult to counterfeit, and consumers need only a smartphone to verify the authenticity.

How would the approach work in the pharma industry?

My little proof-of-concept testing of CandyCodes used actual candy sprinkles because they are already mass-produced and easy to come by. To use CandyCodes on pharmaceuticals for patient use, you'd need to modify a few things; for example, for patients with dietary constraints, using particles that don't contain sugar might be necessary. Also, different markets have different rules on which colorants are approved for food and drug use, so you'd need to make sure that the particles use appropriate colors and dyes for the target market. But I think these are all fairly minor modifications. We'd also need to confirm that CandyCode coatings don't make pills harder to swallow. I tried a few of my CandyCoded pills myself and found that their candy coating made them quite pleasant to swallow (as predicted by Mary Poppins!) but more rigorous testing would be needed.

"CandyCodes are the simplest and most feasible way to put unique identifiers directly onto a pill or other drug product."

Would consumers need to photograph a particular side or angle of their dose?

One of the challenges I faced while developing CandyCodes was how to read the codes. Traditional barcodes and QR codes have a structure and orientation that imparts a meaning to each part of the code, greatly simplifying them. However,

the patterns of colored sprinkles in CandyCodes are totally random.

I solved this problem by taking advantage of how the little colored particles pack together on the surface of a pill. Since the particles are spheres, they tend to cover the surface of the pill in a hexagonal pattern, at least in some local areas. This hexagonal pattern lets us define each sphere's "neighbors" (usually six of them). Then, we can convert that "neighborhood" into a text string based on the colors of the spheres. For example, the text string "WGWWGY" corresponds to a sphere "neighborhood" with a white sphere (W) surrounded by green (G), white (W), white (W), green (G), and yellow (Y) spheres, in clockwise order. Using this process, we can convert each CandyCode to about 50 of these text strings to effectively decode it. These text strings can then be saved in a manufacturer's database of known-authentic CandyCodes and searched when a consumer wishes to confirm the authenticity of a pill.

Crucially, this decoding process doesn't require the CandyCoded pill or capsule to be oriented in a specific way.

Now, if a pill or capsule is completely covered with colored particles, then a manufacturer might need to take photos of each pill from multiple sides to capture all of the CandyCode information. But in my proof-of-concept study, I just coated one side of each pill with colored particles; this approach requires just a single photograph of each pill and still provides more than enough room for each pill to have a universally unique CandyCode. It also leaves the other side of the pill free for conventional brand or dose markings.

I'd love to hear what pharmaceutical producers think about CandyCodes. I've actually already heard from a producer of candy sprinkles about the feasibility of tweaking their production process to make particles optimized for CandyCode use. If a pharmaceutical producer sees any practical problems with CandyCodes, I'd be grateful to hear their thoughts in hopes of resolving those problems in the future. Contact me at *wgrover@engr.ucr.edu*

Reference

1. *WH Grover, "CandyCodes: simple universally unique edible identifiers for confirming the authenticity of pharmaceuticals," Scientific Reports (2022). DOI: 10.1038/s41598-022-11234-4*

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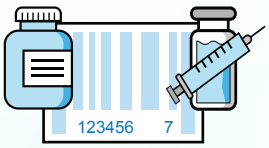

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Breaking New Ground in IBD Research with Organ-Chips

How modeling complex human immune responses in the Emulate Colon Intestine-Chip could give researchers the answers they need to develop breakthrough treatments for inflammatory bowel disease

Emulate's new immune cell recruitment application for the Emulate Colon Intestine-Chip (1, 2) demonstrates the power of being able to explore complex immune responses with unprecedented physiological relevance. Chris Carman, Emulate Director of Immunology, tells us more.

What is immune cell recruitment?

Our immune system monitors for signs of danger, damage, and infection. Immune cells travel through the bloodstream until they are recruited to enter infected tissue, where they respond to the infection, clear it, heal the tissue, and then either die or return to the bloodstream. It is very important that this process is tightly regulated and self-limited; if it weren't, we'd suffer from all kinds of autoimmune diseases starting at a very early age. So, for the immune system to function properly and to maintain health and homeostasis, the selectivity of immune cell recruitment and response is essential.

Why is immune cell recruitment important when researching a disease like inflammatory bowel disease (IBD)?

For the vast majority of us, the immune system functions as it should, with immune cells traveling to a particular location with a specific purpose. When their job is complete, the immune cells clear out and the inflammation subsides. But for those afflicted with inflammatory bowel disease (IBD), the process becomes dysregulated and immune cells are excessively recruited to unintended locations. And that results in further dysregulated immune cell recruitment and reactions, triggering a vicious cycle of pro-inflammatory responses that ultimately cause tissue damage and dysfunction, leading to disease.

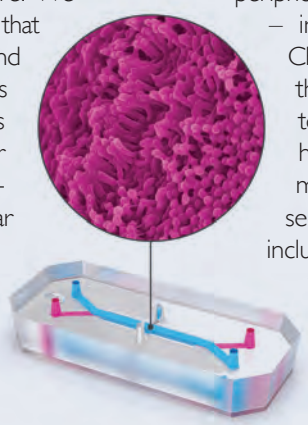
Dysregulated, excessive inflammation is at the heart of most major human diseases. IBD is an excellent example of a disease that depends on – and is ultimately driven by – excessive, dysregulated immune reactions.

How is Emulate's work helping to unravel immune cell recruitment and IBD?

IBD is a complex, chronic disease that is incredibly difficult to study. Its hallmark – the disruption of the epithelial barrier – causes materials inside the intestine, including bacteria, to leak, which then kicks off a subsequent escalation and vicious cycle of inflammation.

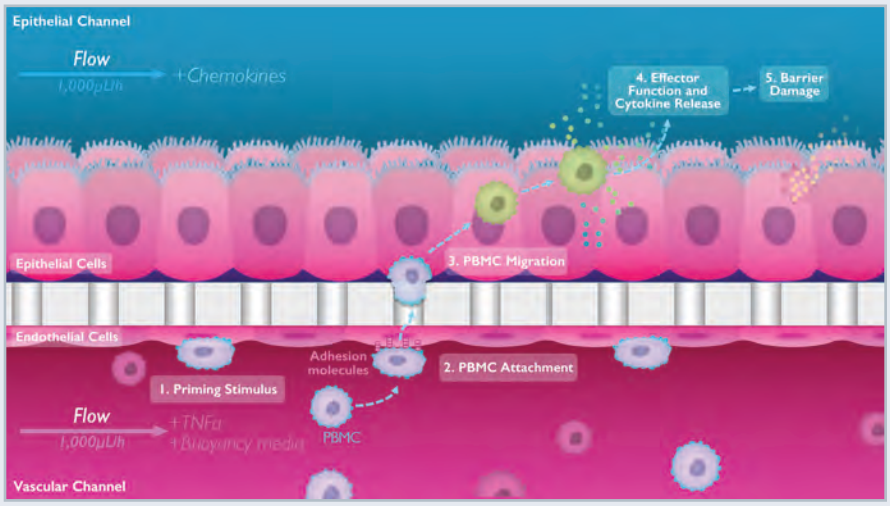
At Emulate, we have modeled the entire process – something that is unprecedented. As inflammation begins, there is always a priming cue that causes local tissue to undergo changes, including critical pro-inflammatory reprogramming of endothelial cells lining the blood vessels. Our model begins precisely at this priming step, and then goes on to capture the full course of disease progression.

To develop this application, we used the Colon Intestine-Chip – a primary human cell model of the colonic barrier that co-cultures organoid-derived epithelium with colon-specific vasculature. We demonstrate in published work that the morphology, function, and transcriptome signature of this model very closely recapitulates human physiology in a manner that is dependent upon the cell-cell interactions with vascular endothelial cells (3). This feature is unique to this model; competing technologies, such as organoid-based approaches, lack vasculature.



To initiate inflammation, we applied a well-established cytokine – a priming stimulus for driving early IBD progression. Critically, we next introduced immune cells – specifically, peripheral blood mononuclear cells – into the Colon Intestine-Chip's vascular channel. With this step, our model was able to capture the complexity of human pathophysiology and mimic most of the critical sequence of events for IBD, including immune cell adhesion to the endothelium and migration into the tissue,

"The truth is that dysregulated, excessive inflammation is at the heart of most major human diseases. IBD is an excellent example of a disease that depends on – and is ultimately driven by – excessive, dysregulated immune reactions."



activation of complex interstitial immune signalling networks, and finally a release of the critical hallmark cytokines and disruption of the epithelial barrier.

How will this model benefit IBD research?

First, and crucially, the Colon Intestine-Chip represents a more complete and complex model of both human intestinal physiology and disease; we believe that this unprecedented completeness – coupled with experimental tractability – will lead to a deeper mechanistic understanding of IBD. Second, and equally as important, we believe this model will enable researchers to identify new therapeutic IBD targets more precisely, so that better and more effective therapeutics can be developed and validated. Ultimately, we hope our model will help researchers greatly diminish the attrition rate of drugs moving into the clinic.

How do traditional models of IBD compare with Emulate's Organ-Chip model?

Traditional models used to study IBD and develop therapeutics for the disease have yielded significant knowledge, but they also exhibit important limitations. For example, conventional *in vivo* studies are almost always performed in mice, which suffer from species-specific differences – a factor that is particularly important when studying the immune system. At the same time, traditional *in vitro* models (whether epithelial cell lines or organoid cultures) are highly constrained by their limited complexity. Each of these models has strengths and weaknesses, but they are really only able to look at one piece of the puzzle, and none capture the full complexity of human disease. As such, researchers can only capture a subset of therapeutic targets with these models. Because the Colon Intestine-Chip and immune cell recruitment application capture a more complete sequence of events for IBD, researchers can study a much broader spectrum of disease targets and, subsequently, develop more effective therapeutics.

Beyond the immune cell recruitment application, how else can Organ-on-Chip technology be used for immunology?

In addition to modeling circulating immune cell recruitment, researchers can incorporate so-called resident immune cells – which also play essential roles in driving immune response – into organ-Chip models. A couple of our developed models apply this functionality today; for example, the Liver-Chip incorporates Kupffer cells to enable studies of immune-mediated toxicity of drug candidates (4); and the Brain-Chip incorporates microglia to enable studies of neuroinflammation – a process that is implicated in many neurodegenerative diseases, including Alzheimer's and Parkinson's disease (5).

Researchers at the Wyss Institute have also modeled the immune system by creating a Lymphoid Follicle-Chip (6), which they have used to recapitulate human immune function, and evaluate the efficacy of vaccines for flu and COVID-19.

How can researchers gain access to these new capabilities and use them in their own work?

First, researchers can work with our in-house service team of experts, who can design and execute a study to investigate the efficacy or toxicity of anti-inflammatory drug candidates for IBD. Second, they can bring Emulate Organ-on-Chip technology – which we call the Human Emulation System® – into their own labs (7). We offer instrumentation to automate cell culture conditions, Bio-Kits that include the chips and primary human cells customers need to build the Colon Intestine-Chip, and robust protocols, training, and experimental support to help drive success. Whether the research is performed in our labs or in our customer's labs, our hope is that these new capabilities can help researchers develop more effective therapeutics for IBD.

References

1. *Emulate, "Modeling Inflammation-Specific Immune Cell Recruitment in the Colon Intestine-Chip," (2022). Available at https://bit.ly/3QJAZO6*
2. *Emulate, "Colon Intestine-Chip," (2022). Available at https://emulatebio.com/colon-intestine-chip*
3. *A Apostolou et al., CMGH, 12, 1719-1741 (2021). DOI: 10.1016/j.jcmgh.2021.07.004*
4. *Emulate, "Liver-Chip," (2022). Available at https://emulatebio.com/liver-chip*
5. *Emulate, "Investigating key mechanisms of Parkinson's with an αSyn fibril-induced brain-on-a-chip model," (2022). Available at https://bit.ly/3OnhHGw*
6. *Wyss Institute, "The immune system is very complicated, but now, it's on a chip," (2022). Available at https://bit.ly/3Hv30ih*
7. *Emulate, "A complete Organ-on-a-Chip solution," (2022). Available at https://emulatebio.com/human-emulation-system*

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Protect the Virus!

Viral vectors can enable innovative medical treatments, but only if we address the unstable elephant in the room with a comprehensive formulation development plan

By Gideon Kersten, Scientific Reviewer and Advisor for Coriolis Pharma and an Extraordinary Professor of Vaccine Development, University of Leiden, Daniel Weinbuch, Business Development Manager for Coriolis Pharma, Tim Menzen, Chief Technology Officer at Coriolis Pharma and Andrea Hawe, Chief Scientific Officer at Coriolis Pharma

Viable viruses are an important group of biopharmaceuticals – and likely the oldest. As early as the 16th century, the practice of variolation was applied in India to combat smallpox. Dried pus from pustules from smallpox patients was administered to the skin of healthy people, unknowingly using viruses as medicines. This primitive and dangerous form of vaccination with a crude preparation of live smallpox virus provided some protection against smallpox. At the turn of the 18th century, Edward Jenner described the potential of less dangerous cowpox material to protect against smallpox. A century later, Louis Pasteur pioneered attenuation of infectious agents, including viruses, to use them as vaccines. All this is remarkable, when you consider that viruses were not discovered until the 1930s, when the development of filters allowed us to isolate viruses and the invention of the electron microscope finally allowed us to visualize them.

Since the 1990s, the use of viruses as gene delivery vehicles has taken off; hundreds of clinical trials have been performed and several dozen gene therapy products are now approved – and many of them use viral vectors. These can be applied directly to the patient (in vivo gene therapy) or used to transfect cells outside the body of the patient (ex vivo) before being returned to the patient.

A third therapeutic application of viruses is tumor targeting. Oncolytic viruses are made native or modified to specifically infect and destroy tumor cells and/or to stimulate anti-tumor immune responses. Several such products have been marketed since the first therapy, Rigvir, was approved in 2004 in Latvia, and numerous clinical trials are ongoing.

The origins of virus instability

As with all complex biological systems, viruses are intrinsically unstable. The loss of viability observed for viruses can be caused by:

1. Protein deterioration that prevents the binding of the virus to the receptor and/or destabilizes the protein capsid in the case of non-enveloped viruses. For instance, after a short treatment of poliovirus or vaccine at 56 °C, the structure of the capsid changes, resulting in virus-like particles that can no longer bind to the receptor.
2. Damage to genetic material (DNA or RNA). RNA is particularly prone to hydrolysis in the presence of water, and at elevated temperatures it may lose the critical secondary structure of its regulatory elements.
3. Damage to the lipid membrane in enveloped viruses. For instance, the stability of retroviruses depends on the composition of the viral membrane, and therefore on the type of production cell line used (1).
4. A combination of all the above. For example, the viral genome is protected not only by a proteinaceous capsid and/or a lipid envelope, but may also contribute to the structural integrity of the virus (2). Therefore, the size of the genome of a viral vector should not be very different from the native genome. Also, the manner in which the DNA is packaged – dense or less dense – has an impact on the viral vector's stability. Higher 'DNA pressure' may result in less stable virus and, as a result, lower infectivity (3).

The relative contribution of these factors to virus destabilization during processing (for example, freezing or drying) and storage is not well understood (4). But it is probably safe to say that viruses can and will deteriorate in any number of ways.

The development of stable virus formulations intended for human application first requires a clear target product profile (TPP) that defines, among other things, the route of administration, dosing, and primary packaging. Second, scientists must establish a set of stability-indicating and phase-appropriate analytical methods to identify and monitor critical degradation pathways and prove activity of the virus. Third, the laboratory infrastructure and analytical methods need to fulfill certain biosafety regulations for virus-based medicinal products; often a biosafety level (BSL) 2 is required. Last, but certainly not least, scientific expertise and prior knowledge in developing virus formulations and setting up analytical methods is extremely beneficial.

Liquid formulations – keep it cold!

The poor stability of viruses is the reason why the majority of currently licensed virus-based products are stored as frozen liquids at -20 °C or even lower temperatures. A few – Zolgensma is one example – can be stored at 2–8 °C for around 14 days. Oral polio vaccine is reasonably stable at 2–8 °C, but for storage periods exceeding 6 months, -20 °C or lower is advised.

As freezing may cause dramatic changes in ionic strength, osmolarity, and pH, the sensitivity of viruses to these effects should be investigated during formulation development, making it possible to select suitable conditions with respect to pH, buffers, and excipients. In addition, the effects of final storage temperature, freezing speed, thawing procedure, and so on should be determined experimentally. Knowing the physical state of a frozen solution as a function of temperature is important. Phase separation and other inhomogeneities in the matrix may occur during freezing. At moderately low temperatures such as -20 °C, solutions may not be completely frozen, leaving room for molecular mobility and chemical deterioration. Crystallization events and freeze concentration of excipients during freezing can damage the virus. Differential scanning calorimetry (DSC) reveals some of these effects and can help to select optimal freezing and storage conditions. In general, fast freezing rates are beneficial because they promote the formation of amorphous glasses instead of crystallized solids. In the case of enveloped viruses, fast freezing may avoid formation of lipid membrane damaging ice crystals (4).

Your selection of buffer and cryoprotectant is particularly important. Phosphate-based buffers may induce very considerable pH shifts of several pH units during freezing because of separate crystallization of the buffer salts. The main cryoprotectant groups are sugars, sugar alcohols, and alcohols.

The development of effective formulations often has a highly empirical nature. It is all but impossible to reliably predict the optimal compositions or concentrations of stabilizing excipients. The number of variables is large (consider type and concentration of excipients, freezing rate, thawing rate, combined effects of excipients, and so on), making it hard to perform extensive screenings that cover all aspects.

Therefore, a systematic and stepwise approach is highly recommended to generate a scientific understanding and to de-risk the development: starting with a pH/buffer screening, followed by an excipient screen with a selected cryoprotectants and other stabilizers, followed by an optimization phase in which, for instance, different excipient concentrations are tested. One complication with frozen liquid formulations is that accelerated stability studies are intrinsically impossible. Time-consuming real-time stability studies (apart from repeated freeze-thawing) are therefore the only way to assess stability. Despite these challenges, having experience in formulation of different viruses is beneficial to the setup of a scientifically sound and knowhow-driven formulation development

Category of assay	*Name of assay*	*Target information*
Functional (potency)	Cell transduction	Ability to deliver gene to cells
	Immunogenicity	Ability to induce an immune response
	Oncolytic potency	Ability to kill tumor cells
Semi-functional (potency-indicating)	Virus titration	Viable virus
	PCR	Genome copy number
Non-functional (quality indicating)	Analytical ultracentrifugation	Particle size of fragments, intact virus and small aggregates, sedimentation coefficient
	Chromatography (SEC, ion exchange)	Size, purity
	FFF-MALS	Particle size, amount, aggregation
	Immunoassay (ELISA)	Amount of viral antigen
	Dynamic light scattering	Virus size, sub-visible aggregates, virus fragments
	Nanoparticle Tracking Analysis	Particle size and particle concentration
	Backgrounded membrane imaging	Subvisible particles
	Electron microscopy	Particle morphology, size
	Flow imaging microscopy	Subvisible particles

Table 1. Examples of analytical techniques for characterization of viruses (5). ELISA: enzyme-linked immunosorbent assay; FFF-MALS: field-flow fractionation with multi-angle light scattering detection; PCR: polymerase chain reaction; SEC: size exclusion chromatography.

approach. Moreover, multi-disciplinary teams of formulation scientists, analytical specialists, and virologists can increase success rates considerably.

The lyophilized "solution"

Supply chains with sub-zero temperatures are not always feasible. If frozen liquid formulations will not work, lyophilization can be used to stabilize the virus – indeed, this process is used for most live attenuated viral vaccines, including vaccines against measles, yellow fever, and rabies. However, it is important to design a formulation that protects the virus against potentially harmful events during freezing and drying. Typically, excipients with cryoprotecting and lyoprotecting activity must be present. Efficient lyoprotectants, such as sucrose and trehalose, are good water substitutes, which maintains conformation of viral proteins in the dried state. Lyoprotectants also contribute to a high glass transition temperature (Tg) of the lyophilized material, which is advantageous for storage. When the product is stored at temperatures above the Tg, the glassy state of the freeze-dried matrix becomes more rubbery, causing increased molecular mobility. In addition, recrystallization of amorphous excipients may occur, which may damage virus particles. Note that even small amounts of residual water will reduce the Tg significantly, rendering the product less stable. In short, it is important to keep water content low and to optimize the lyophilization process accordingly. In fact, the lyophilization process (the unit operation) must be developed and aligned with the formulation development process (the composition). Freezing rate, drying temperatures and pressures, and the application of controlled nucleation to reduce inter-vial differences in freezing rate all need to be considered.

Analyzing virus quality and stability

To assess the effect of formulation and storage conditions on product quality and virus stability, you'll need appropriate analytical assays, which can be categorized as functional, semi-functional, and non-functional (see Table 1). Functional assays measure the potency of the virus, such as its ability to transfect cells or the immunogenicity of a live viral vaccine in experimental animals. These methods are usually time consuming, expensive, and not sufficiently accurate, which means they are less suitable for formulation screening purposes.

Alternative stability indicating assays for viruses are available. Infectivity assays are particularly important because they are semi-functional but less labor-intensive than functional assays. In general, the ability of viruses to infect cells is determined by measuring cytopathic effects (CPE) in host cells incubated with dilution series of the virus. Depending on the virus and the host cells, CPE can range from barely affected host cells to complete cell lysis. Readouts will differ depending on the type of CPE and may include direct microscopic visual assessment of the cells, immune fluorescence in a FACS,

or fluorescent focus assays.

Infectivity assays, although very relevant, are still time consuming and lacking in accuracy. Instead, quantification of gene copy numbers by PCR is often used. This method does not measure viable viruses, but the number of viral genome copies. This may or may not correlate with infectivity.

A third group of assays are non-functional characterization methods. Despite the somewhat unappealing name, these assays can provide detailed information about the structural integrity of viral particles. Assays belonging to this category determine physico-chemical properties, such as particle size measurements by light scattering techniques, size exclusion chromatography, analytical ultracentrifugation, and AF4 (5). If necessary, viral components, such as proteins and nucleic acids, can be analyzed by electrophoresis, HPLC, and spectroscopic methods. The advantage of many of these techniques is that they are high throughput and generally more accurate and sensitive compared with the functional methods. The onset of viral aggregation or loss of virus – for example, due to adsorption – during a stability study is in some cases detected earlier than a statistically significant loss of virus titer. In this way, a more accurate ranking of formulations is possible, which in turn allows for rational selection of the best formulations.

Over the course of virus formulation development, a combination of functional, semi-functional, and non-functional assays is not only recommended – it is required.

We can do better

Formulation development of viral products is still highly empirical and, in our view, often not performed adequately. In that respect, one could argue that not much has changed since the 16th century's variolations! The air-dried material from those times, high in potentially stabilizing impurities, may have been as stable (at least for a short period of time) and effective as some of today's virus formulations.

In many cases, there is room for improvement – particularly when aiming for a high quality product with long-term stability. To achieve this goal, you should not rely on off-the-shelf formulations for the virus of interest and expect them to result in an acceptable stability profile. Viruses are highly sensitive, and – depending on the type of virus – different stability challenges may arise. To obtain a stable product, you must perform dedicated virus-specific formulation development from initial screenings to formulation optimization (including the proper set of analytical methods).

Scientific knowledge about factors influencing virus stability is growing – and so is our collective ability to overcome virus instabilities with science-driven formulation development. In the years ahead, we should be using expert know-how and applying a range of formulation approaches, including lyophilization, to obtain stable and phase-appropriate virus formulations.

See references online at: tmm.txp.to/protct-th-virus

Considering Capsids

Adeno-associated viruses (AAV) are the most popular viral vectors to date for in vivo applications – but determining full versus empty capsids remains a key challenge

By Audrey Chang, PhD, Biologics Executive Director at Charles River

Dr. Audrey Chang has always had a passion for driving high quality science in the regulatory arena with a final goal of providing safe and effective biological products to the public. With over 25 years of government and industry experience in conducting biological products testing and in managing laboratories, she has deep interest in helping the industry move forward, including discussing the present future of determining full versus empty capsids remains a key challenge for the AAV-based gene therapy field.

A 2021 FDA Advisory Committee meeting briefing document showed that 24 percent of gene therapy studies worldwide in 2015–2020 used AAV. Indeed there is a rapidly growing number of clinical investigations and successes – and AAV therapies will undoubtedly move from rare disease indications to more common diseases.

During AAV manufacture, the goal is to produce vectors that contain the therapeutic gene of interest – full capsids, but the process inevitably creates particles that fail to capture the essential genetic information – empty capsids. The percentage of empty capsids can vary from 50–90 percent, and there is also potential for partial sequences or even other variants that package host cell DNA. Right now, the biopharma industry does not fully understand the biology of AAV or what causes the formation of empty capsids – though the manufacturing process certainly plays a role.

So why the concern? Well, empty capsids deliver no therapeutic benefit – and, from a safety perspective, they could increase the risk of heightened immune response from the patient's total capsid exposure from all these particles. Additionally, the potential of illegitimate packaging of host cell genes can be concerning if they package an antibiotic resistant gene or oncogene that will unintentionally be delivered to the patient.

From a regulatory standpoint, manufacturers are expected to account for empty capsids as a percentage ratio of full:empty particles. This requirement is outlined in guidance from the FDA, but the agency does not call out a specific threshold number. Rather, manufacturers must establish their own critical quality attributes to characterize their product and define risk-based acceptable percentage ratio of full to empty capsids in their batches based on data generated from PD, engineering, and manufacturing runs.

Methods used for testing AAV capsids

As an advanced therapy CDMO leader for over two decades, our expert analytical development services team has first-hand experience testing AAV capsid methods, established and emerging, their advantages and limitations.

"Given our extensive experience at Charles River with diverse AAV capsid testing methods, we set out to explore the analytical challenges."

Analytical ultracentrifugation (AUC) is considered the gold standard for determining the percentage of full capsids. In brief, an optical "eye" collects sedimentation velocity profiles over time during the specialized ultracentrifugation run. With this information, it is possible to identify expected peaks of full, empty, and even partially filled peaks. However, it is not a high-throughput method, making it unsuitable for early process development runs or formulation studies.

Transmission electron microscopy (TEM) is a direct visualization method. TEM images – or the newer cryo-TEM images – show empty, full and, to an

% Full

Three methods comparison

	% FULL		
	TEM %	AUC %	QPCR/ELISA %
AAV1 GFP	61.0	94.7	93.5
AAV2 GFP	71.2	93.1	51.3
AAV5 GFP	67.3	88.4	104.4
AAV6 GFP	56.3	85.1	85.2
AAV8 GFP	74.8	88.9	171.8
AAV9 GFP	82.3	92.9	51.0

Assay Overview

Parameters

METHOD	TARGET	REPEATABILITY	TIME	SAMPLE VOLUME	RANGE	KEY ADVANTAGE	KEY DISADVANTAGE
AUC	Particle	2%	6 hr	400 ul	$10e^{12}$ cp/ml	De facto standard and can detect partials	Low throughput, needs purified sample, Instrument
TEM	Particle	15%	3-6 hr	3-20 ul	Unavailable	Direct imaging	Low throughput, needs purified sample/skilled personnel Instrument
ELISA	Capsid protein	10-20%	2-5 hr	100 ul	$10e^{8}$-$10e^{10}$ cp/ml	common method for capsid titer	Serotype specific, labor intensive
PCR	Nucleic acid	5-30%	1-2 hr	1-10 ul	$10e^{5}$-$10e^{10}$ vg/ml	common method for genomic titer	Reliance on standard, sensitive to variability in replication efficiency and matric effects

Source: *"Analytical methods for process and product characterization of recombinant adeno-associated virus-based gene therapies"* Gimpel et al Methods & Clinical Development 20 March 2021

extent, partially filled populations. But, as with AUC, TEM is not high-throughput and requires specialized instruments and skilled laboratory personnel. It's also dependent on critical sample preparation steps.

A popular approach for determining full and empty capsids at the lab-scale combines enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) testing. ELISA looks for the capsid protein, which is present on both empty and full populations, whereas PCR only detects particles that contain the genome and can be used to represent the full population. Although both techniques are highly accessible, the data are less than perfect.

Nevertheless, it is common practice to use methods that offer a more rapid turnaround time in the early stages before switching to more established methods for later phase analysis. However, this "switching" can also be problematic if methods and specifications set with the earlier non-GMP methods do not translate in the established method. Additionally, though there are emerging methods (1-3) with promise, the burden of comparability studies and, ultimately validation, can be a considerable challenge.

A boost to comparability studies

Given our extensive experience at Charles River with diverse AAV capsid testing methods, we set out to explore the analytical challenges, and conducted a comparison study to evaluate these common techniques used to test capsids. The ultimate study goal was to to share our results with the market, showing the critical role of a reference material for product lifecycle.

Using the same AAV manufacturing process performed for our clients, we made reference materials – 12 AAV reference material based on six different serotypes: AAV 1,2,5,6,8, and 9 (six full and six empty). Each lot was issued with data generated from a panel of QC analytical assays, including genomic copies, pH, bioburden, mycoplasma, endotoxin, purity, and percentage of full/empty capsid ratio by TEM.

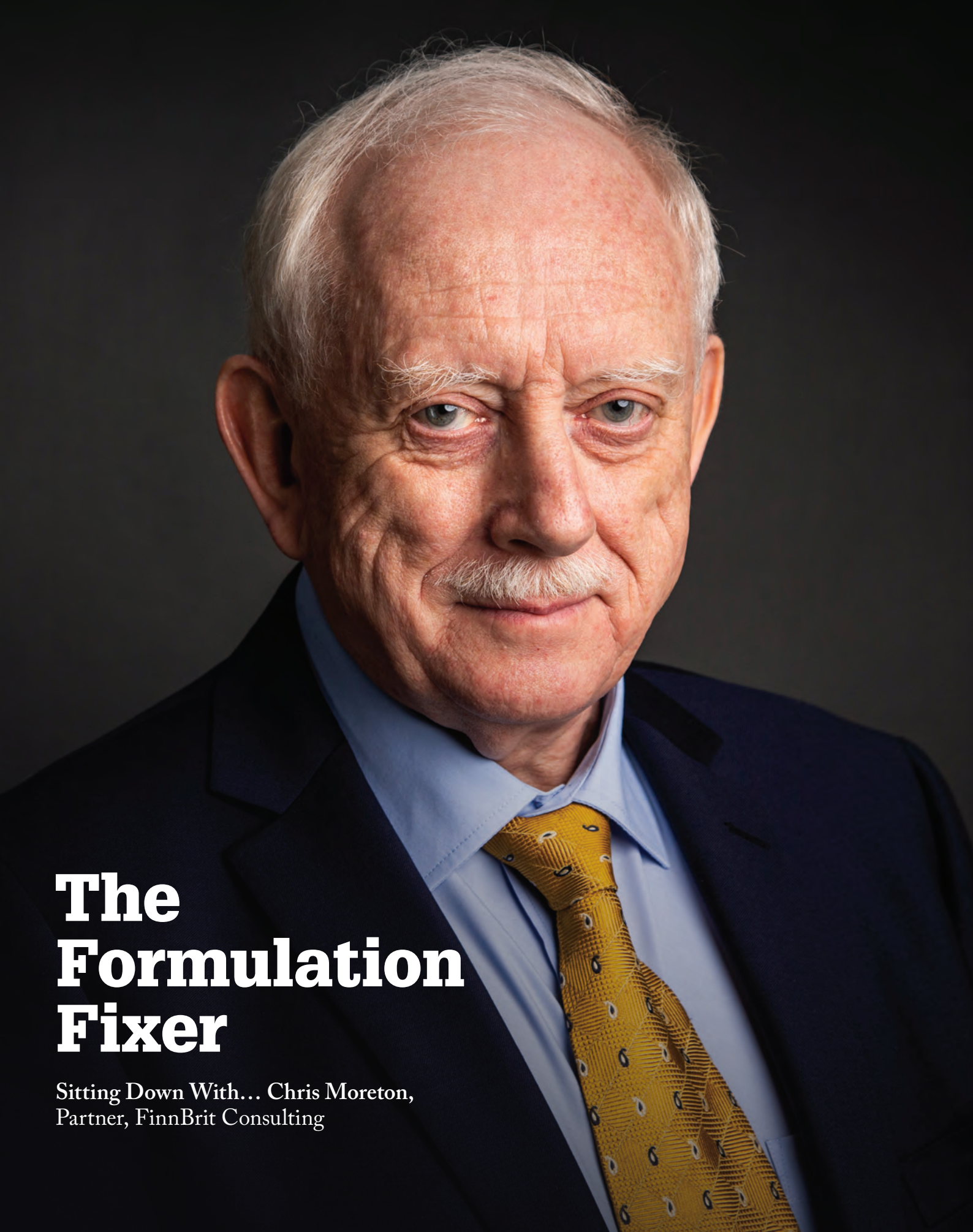
With our reference materials, we performed a side-by-side comparison of the percentage of full/empty capsids with TEM, AUC and PCR/ELISA. The AUC percentage full numbers for AAV reference material were higher in value compared with TEM – and also closer in agreement than to PCR/ELISA. PCR/ELISA showed much higher variability and less reliability – not unexpected given that these methods are indirect.

Our comparison study really showcases how reference materials can be used to demonstrate comparability between different methods. Having a reference standard and/or reference material enables the translation of data from development, comparability studies, validation/revalidation, technical transfer, and assay trending. Reference standards also allow for well-designed bridging studies for future versions of the process. And so you may be pleased to know that we've made these reference materials for AAV 1,2,5,6,8, and 9 (six full and six empty) available to our clients to help generate data for both today's and tomorrow's analytics.

To get the full details of our Empty vs. Full AAV Capsid Analysis, watch our webinar: https://bit.ly/3AX9s0g: Empty vs. Full AAV Capsid Analysis: A Comparative Study Using AAV Reference Materials.
To learn more about our AAV products, visit us at: https://bit.ly/3zGZBcQ

References

1. *AL Gimpel et al., Molecular Therapy: Methods and Clinical Development, 20, 740-754 (2021). DOI: 10.1016/j.omtm.2021.02.010*
2. *AK Werle et al., Molecular Therapy: Methods and Clinical Development, 23, 254-262 (2021). DOI: 10.1016/j.omtm.2021.08.009*
3. *Yang et al Gen BioTechnology (2022)*



The Formulation Fixer

Sitting Down With… Chris Moreton,
Partner, FinnBrit Consulting

What inspired your interest in science?

My father, who was an organic chemist. He worked for ICI, a company that no longer exists. He worked there all of his working life apart from his military service in WW II. I was always interested in science, but my father's one regret was that I never really got on with organic chemistry! Originally, I went to undergraduate school to study biochemistry, but that changed for various reasons and I ended up studying pharmacy.

How did you get into industry?

On leaving pharmacy school, I first worked in the hospital service as a trainee pharmacist. I was, quite frankly, unimpressed! I was counting medicines and that was it – and I felt it would drive me mad! I decided to switch to industry. I got a job with a small CMO, which fortunately doesn't exist anymore, because it was a dump! (This was in the days before GMP was mandatory in the UK; the first GMP inspections in Britain didn't happen until the summer of 1972.) I stayed on at the company after completing my registration as a pharmacist. After my boss moved to another position, I was promoted to Chief Pharmacist. We received a letter from the Medicines Control Agency (now the MHRA) notifying us of our next GMP inspection, and referencing a previous letter that required the company to do certain things. I took the letter to the general manager, and asked to see the letter from the previous year. None of the action points in that letter had been addressed, but his thinking was that we'd gotten away with it until now, so why change? I handed the letter back to him, walked back to my office, and started looking for another job. That was not the type of company I wanted to work for.

Why formulation?

I've always enjoyed formulation work. In fact, I'm also fascinated by it! I also had a knack for finding solutions, but not necessarily with the tools people wanted me to use. For example, some companies have set management and research tools. On more than one occasion, I found a solution to the problem that using the tool did not achieve!

In some cases, the tools worked well for synthetic chemistry, but not so well for pharmaceutics. In the early days of my career, there was also a lot we didn't know about formulation. There is still a lot we don't know. For example, two of the most commonly used excipients are magnesium stearate and microcrystalline cellulose and we still don't know nearly enough about how and why they work – despite the fact that they have been used for decades.

How did you get involved with IPEC-Americas?

In the early 1990s, I was working with an excipient company in Britain. After IPEC Europe was founded, my then boss thought it was important to work with them, and he delegated me as the company representative on an IPEC Europe committee (they only had two committees back then!). I would attend meetings and we would evaluate proposals from the Pharmacopoeias for monograph harmonization. When I transferred to the US, my boss wasn't really interested in IPEC – he wanted to go out on the road and promote the company's products – so the job was delegated to me.

Many key people in IPEC are on the regulatory or quality side, but I bring a different perspective because of my experience in formulation. I was the chair of IPEC-Americas from 2003 to 2004. I am very interested in the performance of excipients and I've been working with USP on excipient-related expert committees since 2000.

What are the biggest formulation challenges today?

The biggest issue is poor water solubility. Many compounds are just very insoluble and sometimes formulators also need to deal with a high partition coefficient as well.

There is a reason solubility is still an issue after all these years. Back in the 1970s, when I was at Pfizer, we didn't have many poorly water-soluble compounds in the pipeline because the pharmacological screens we used to evaluate new molecules couldn't handle them, so they weren't active in the screens. But today, changes in chemistry, better understanding of drug-receptor interactions, and high-throughput screening for pharmacological activity have taught us that useful molecules are often hydrophobic. When we bolt new groups onto the molecule to interact with a specific receptor site, we add more molecular weight, and often more hydrophobicity, both of which drive solubility down further. It's estimated that around 70 to 80 percent of new drugs going into development are poorly water soluble.

Figuring out which formulation option is the best for a molecule is a major area of interest for me.

If you could change one thing in the industry, what would it be?

Actually, I'm going to say two things. One, I would very much like the FDA pilot program for novel excipients to succeed and become permanent. IPEC-Americas is very passionate about this program and its importance to the industry. Novel excipients will lead to improved formulations. And two, I would like more pharmaceutical production to be brought home. Some organizations overseas do a good job in manufacturing. Others try to do a good job – but do not always succeed. Some deliberately try to cut as many corners as they can. For example, there have been a lot of quality issues in certain countries – something that was highlighted in presentations at the recent Excipient World Conference in Kissimmee, FL. In some cases, people are too fixated on price, which can lead to quality issues. For the safety of patients, we need to focus more on quality and ensure that standards of good manufacturing practice are not compromised.

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