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24 – 32

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Online this Month

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Find out more about Team Medicine Maker by following us on Twitter!

@medicine_maker

The flagship account for The Medicine Maker team will keep you up to date with our latest articles, events, and promotions.

@SJC_Sutton

Our Editor, Stephanie Sutton, tweets about conferences, science news, health, homeworkers, and the occasional dog photo from her home office.

@J_Strachan_Edit

Deputy Editor James has been diligently following Brexit and the impact it may have on the pharma industry; follow him to keep up with the latest political talking points.

@PublishingRick

The esteemed Publisher of The Medicine Maker tweets about everything from events and happenings at The Medicine Maker, to fascinating science facts, to marketing, and more.

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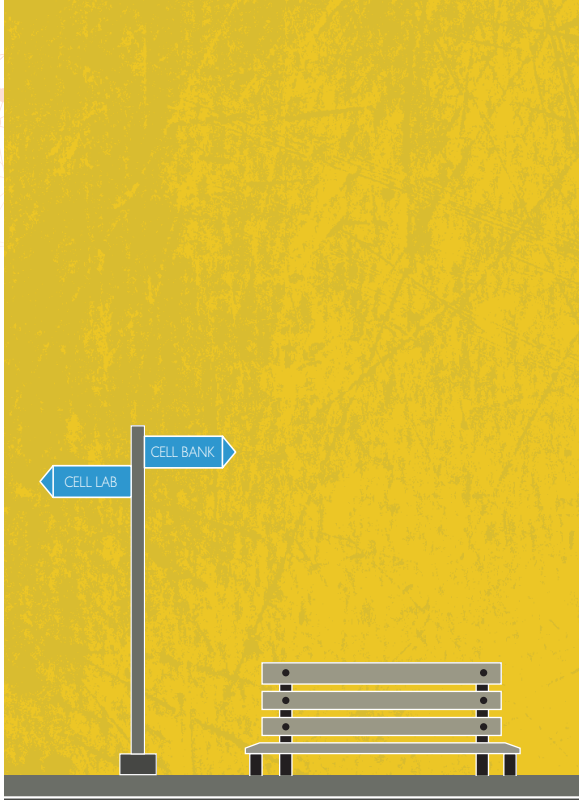

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On The Cover

The dilemma of choosing between mother's health or baby's health.

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the **Medicine Maker**

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Change of address:
info@texerepublishing.com
Hayley Atiz, The Medicine Maker, Texere Publishing, Haig House, Haig Road, Knutsford, Cheshire, WA16 8DX, UK

General enquiries:
www.texerepublishing.com
info@texerepublishing.com
+44 (0) 1565 745200
sales@texerepublishing.com

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A (Pregnant) Pause For Thought

It's time for maternal health to escape from the dark ages, and pharma has a duty to help.

Recently, The Medicine Maker has published numerous articles discussing the future of pharma and the role that new "Industry 4.0" technologies can play. Big data and AI, for example, could have a huge impact on drug discovery (1,2), and at the recent CPhI trade show in Madrid there was an enormous focus on technologies that enable continuous processing and continuous bioprocessing. In previous issues, we have also written about smartglasses that empower workers in new ways (3), and 3D printing technologies (4). The amount of technology at pharma's disposal is truly staggering. A number of cutting-edge themes also feature in our October issue. On page 10, researchers discuss the use of computer simulations for reducing side effects, and on page 19, Kal Patel looks at how pharma can use digitization to benefit patients.

But if industry 4.0 is the future of pharma, I don't think it's too much of an exaggeration to say that the current approach to drugs for use during pregnancy and lactation is the polar opposite. It's an area of medicine still trapped in the dark ages – and the subject of this month's cover feature (page 24). Too often, risks to the developing fetus or baby are thought to be too high a price to pay to study or treat pregnant and lactating women. But the lack of information leaves many women with an impossible choice to make: stop taking a much-needed medication and risk the health consequences, or continue with it and face unknown risks to the unborn or newly born child. I spoke with doctors who are struggling to treat their patients, a representative of Duchesnay (a pharma company with a special focus on drugs for maternal use), and to researchers who have worked on PRGLAC – a US taskforce dedicated to addressing the knowledge gap. The message? Change is coming.

This topic has recently (over the last 8 months or so) shifted from the purely theoretical to the highly relevant for me; my first child is due at the end of October. Despite being in relatively good health, I have certainly faced tricky decisions on whether to take basic OTC medications (or not). But for women with serious and chronic conditions that require medication, change simply can't come fast enough. I hope pharma continues to work on the means to "deliver" to us all.

Roisin McGuigan
Deputy Editor

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Upfront

Reporting on research, personalities, policies and partnerships that are shaping pharmaceutical development and manufacture.

We welcome information on any developments in the industry that have really caught your eye, in a good or bad way. Email: stephanie.sutton@texerepublishing.com

Courtesy of Diamond Light Source.

Source of Light – and Inspiration

A new center for electron bio-imaging was officially opened by one of the three Nobel Prize winners behind the cutting-edge technology at its heart

While the world hurries to congratulate the 2018 Nobel Prize winners, we're still celebrating Richard Henderson, who, along with Jacques Dubochet and Joachim Frank, won the 2017 Nobel Prize in Chemistry "for developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution (1)." Why? On September 12, 2018, Henderson officially opened Diamond Light Source's electron bio-imaging centre (eBIC) in Cambridge, UK. The event coincided with the announcement of a partnership between Diamond and Thermo Fisher Scientific, which adds two new microscopes and professional cryo-EM services specifically for the pharmaceutical industry.

The additional capacity makes eBIC one of the largest cryo-EM sites in the world – a true nod to the technology's fast-growing significance in structural biology. Rich Whitworth, Content Director of The Medicine Maker, was given the opportunity for a brief one-on-one with the Nobel laureate.

Forgive the obvious question, but how did it feel to win "the prize" in science?

Obviously, it's a great honor. The Nobel Foundation has a great impact on the world, and it really raises the profile of science a great deal. However, I have to say, we were not entirely surprised – and I'll tell you two amusing stories that got me thinking… First, in 2013 or so, when we started to get really good results with cryo-EM, my students kept asking me, "Do you think you will get a Nobel Prize for this?" I answered by saying it was "a bit of a lottery." Second, on the Thursday afternoon at the end of our 2016 annual cryo-EM meeting, the closing pantomime sketch featured a "wheel of fortune" that could predict the next Nobel Prize winner; because it was a cryo-EM meeting, five of the six spots on the wheel were dedicated to "Cryo-EM," the sixth slot was reserved for "CRISPR/CAS 9." In the sketch, the wheel was spun several times, but the arrow always landed on "CRISPR-Cas9," much to everyone's amusement. No Nobel Prize for cryo-EM! Of course, as it turns out, cryo-EM did win a year later…

You've been working on cryo-EM for many years – has progress been as rapid as you expected?

It's been much slower than we thought. Scientists, generally speaking, are optimists. If you're a pessimist, you probably shouldn't do research because you'll always expect to fail – perhaps try the insurance industry. I was originally in X-ray crystallography and then electron crystallography, and then, about 20 years ago, I decided that single-particle cryo-EM had a great future. We started experimenting and we thought we'd have it all done by the end of the year – that was

1997 or so. But there were all sorts of problems that had to be tackled one by one. The microscopes and the computer programs certainly improved over the years, but it was the development of new detectors around five years ago that really took us over the hump. Today, it's much better than it was five years ago, and in another five years it will be better still. It will be faster, the data will be better, and it will provide higher resolution with less effort. It's really quite a positive atmosphere at the moment in this area of structural biology.

Do you think cryo-EM will supplant X-ray crystallography for structural biology?

I don't think it will fully supplant current methods, but it will become the number one choice in some cases – particularly when it comes to structures with difficulties; for example, issues with stability, purity, or conformational heterogeneity. The synchrotron-based experiments will continue – they allow us to collect 300 datasets per day, whereas with cryo-EM it's currently one. But the technology will improve, and I see no reason why we can't get to 300. In the coming years, we will know the structure of virtually every molecule in biology that we're interested in. But there will still be plenty to do. If we could design one drug to activate and one drug to inhibit every one of those molecules, we'd be in a very powerful position.

For more about Diamond Light Source and eBIC, visit www.diamond.ac.uk

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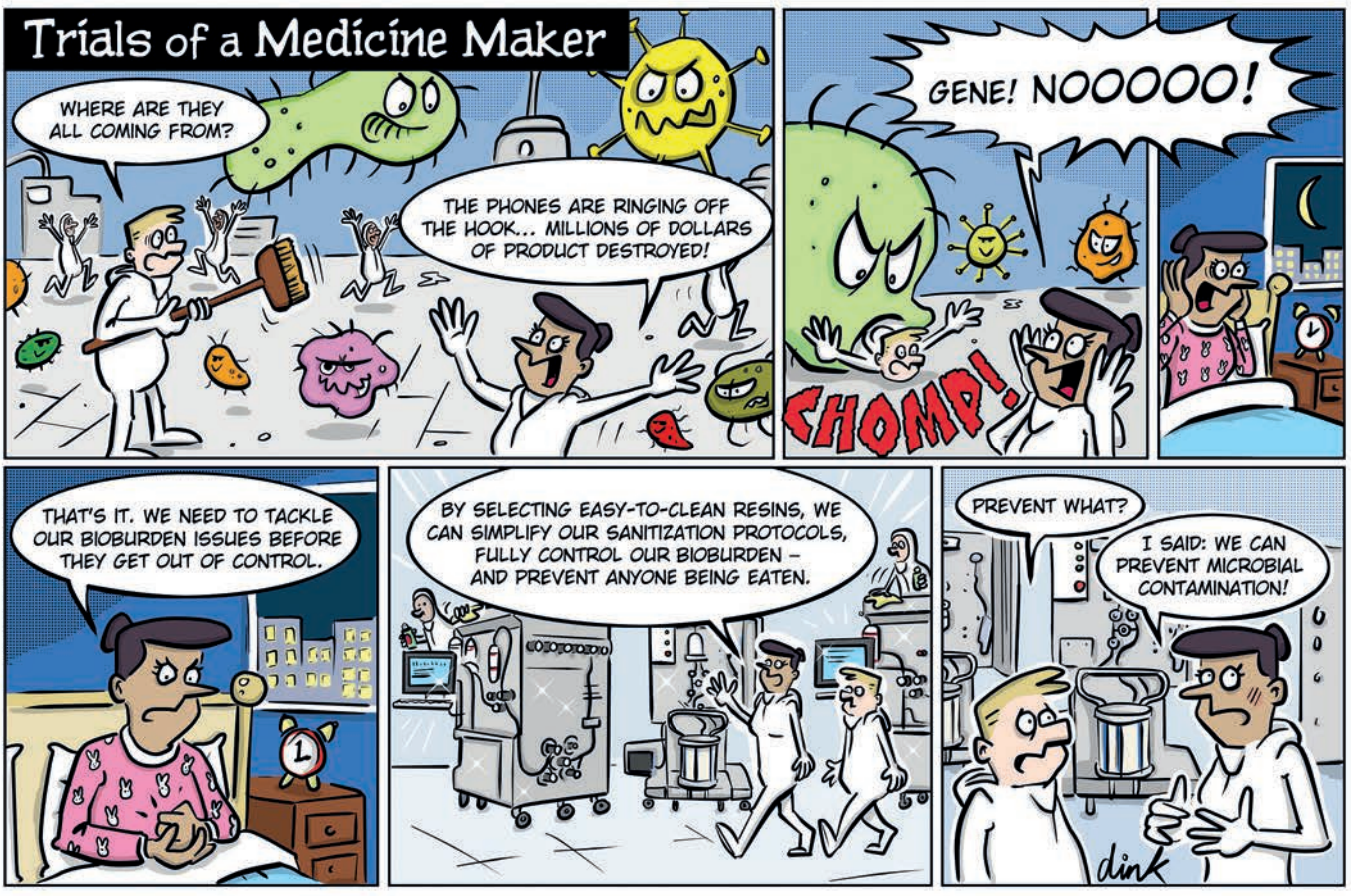
For more adventures featuring Gene and Eva check out our website themedicinemaker.com/additional-data/cartoons
If you have any ideas you'd like to see in future comic strips about bioprocessing then get in touch with us at info@themedicinemaker.com or look up #TrialsOfAMedicineMaker on Twitter.



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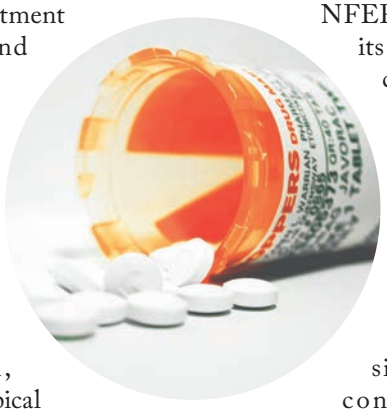
Eliminating Side Effects In Silico

Next-generation pain medications developed with computer simulations could improve on current opioid offerings

"My group has studied the biology and pharmacology of opioid receptors on peripheral sensory neurons for over 25 years", says Christoph Stein, Director, Department of Anesthesiology and Surgical Intensive Care Medicine, Charité – Universitätsmedizin Berlin. "Our aim has always been to find mechanisms and opioid receptor ligands that can be developed into drugs which inhibit pain, without also eliciting typical adverse effects of conventional opioids, such as apnea, addiction, sedation or constipation."



"From our previous work we knew that selective activation of opioid receptors can produce powerful pain relief. These analgesic effects are particularly strong in pain caused by tissue injury and inflammation. So, together with mathematicians at the Zuse Institute Berlin, we began using computer simulations to examine the interaction between opioid ligands and receptors in normal and inflamed environments," says Stein. The group discovered that low pH – as found in damaged/inflamed tissue – led to stronger binding of opioid ligands to peripheral opioid receptors. To benefit from this effect, the team designed a new compound – called NFEPP – that, because of its low acid dissociation constant, selectively activates peripheral μ-opioid receptors (MORs) at lower pH, limiting its effect to injured tissue (1-3). "These new compounds avoid the detrimental side effects of both conventional opioids and nonsteroidal analgesics," adds Stein.

Stein is aware of his group's potential contribution to a solution to the opioid crisis in the US – but cautions that new drugs alone are not the answer: "Improved pain medication will not erase this crisis; that will require joint efforts by politicians, medical societies, healthcare providers, insurers, researchers and the pharma industry. However, new drugs without deleterious side effects will be an important step in the right direction."

The team now plans to investigate the interaction of opioid ligands and receptors in inflamed environments in more detail, and is seeking partners or investors from pharma to push their new compound towards phase I and II clinical trials.

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The Deadline for Innovation

Nominations for The Medicine Maker's annual Innovation Awards will close on Tuesday November 6, 2018

What?
Our annual Innovation Awards are an opportunity for vendors of bio/pharma development and manufacturing solutions to strut their stuff! The Awards will showcase some of the best product launches of 2018 that have made a difference to manufacturers' lives. Previous winners of the Innovation Awards have included:

- 2017: A challenge agent for H3N2 developed by SGS to accelerate the clinical development of influenza vaccines.
- 2016: Centinel (Merck KGaA), which used gene-editing technology to make CHO cells resistant to Minute Virus of Mice.
- 2015: Open Innovation Platform (LEO Pharma) – a truly open innovation platform designed to bolster research in dermatology.

Why?
When thinking of innovation in the pharma industry most people think of amazing new medicines, but behind every medicine is a swathe of equipment and processes. New medicines could not be made without innovation in development and manufacturing technologies. The Medicine Maker Innovation Awards puts vendors and their incredible dedication to progress in the spotlight.

How?
All you need to do is fill out the quick online form. Our judging team will need to know the name of the innovation, and some brief details about what it is, why it's so innovative, and how it can potentially impact bio/pharma development and manufacturing. For example, could the innovation accelerate timelines? Lead to a new frontier of drug development? Solve significant challenges in the manufacturing environment? We consider all innovations, including equipment, software, instruments, technology or even a service relating to any area of drug development, manufacture or formulation.

To be eligible, the product's launch date must be during 2018 (January 1, 2018, to December 31, 2018).

Where?
You can find the online form at: https://bit.ly/2Ckaoxt

Or get in touch with the Editor, stephanie.sutton@texerepublishing.com.

When?
Nominations will close at midnight on Tuesday November 6.

Fifteen shortlisted innovations will be announced and showcased in the December issue of The Medicine Maker. A public vote will open in late 2018 to decide the grand winner.

Due to the number of entries received, we will only contact shortlisted entries.

Bearfaced Research

A new method for discovering antibiotics makes use of an unusual source of complex microbial communities

A team of scientists has developed a technology that rapidly assesses antibiotics using microbes from a curious source: saliva taken from the East Siberian brown bear. We spoke to co-author of the associated paper (1), Konstantin Severinov, a professor based in the Waksman Institute of Microbiology at Rutgers University, to discuss antibiotic screening – and how to catch a drooling bear…

Why use bear saliva?

We are part of a long-term expedition to Kamchatka, so a bear was a natural choice – bears have a diverse diet, so we assumed that their microbiome will also be diverse. They also have lots of drool! The challenge, of course, was to catch one. A trained hunting husky was used to lure a bear into a cage. Once inside, it was offered a stick covered with absorbent canvas, which it duly bit, and there was plenty of saliva to pack into test tubes once it let go. It did get some honey as a consolation prize, and was released again with the help of the husky.

How does the method work?

Current procedures for screening microbes for antibiotic production are tedious and require testing individual isolates one by one. The power of our procedure is that microbes from various communities (in our case, the oral cavity of a wild bear) are cultivated in oil drops filled with nutritious medium, where they are isolated from each other and cannot affect each other's growth. In the presence of a target microbe

– in our case, Staph aureus, which had been made fluorescent with a green protein – we can detect the effect of these droplet-incarcerated microbes on growth.

We can sort the droplets at tens of thousands per minute using fluorescence activated sorting to isolate droplets (and the microbes contained in them) with lower florescence, where Staph growth is inhibited, presumably because of some noxious compound produced by the microbe. Our method still depends on cultivation, which is a major limitation, as most microbes are not easily cultivated in the lab.

What impact does the method have on the discovery of new antibiotics?

The throughput of our procedure should allow scientists to screen orders of magnitude more microbiota cells, and hopefully find new antibiotic producers. Once identified with our procedure, there will be the "normal" workflow of identifying the compound, determining its structure, genes responsible for its synthesis, spectrum of antibacterial action, and so on. We also think that the procedure could easily be applied to rapidly determine the susceptibility of microbes in a community to a particular drug – we describe this in more detail in our paper (1): you essentially load droplets with microbes, nutritious medium, and various concentrations of an antibiotic or a control. For strains that are susceptible to the antibiotic you test, you will see depletion in representation after growth.

Next, we plan to apply our procedure to microbiota from other microbial communities – both "exotic", such as a Komodo dragon, and "standard" (human), to hopefully find new antibiotic leads.

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The True Cost of Falsified Medicine

A recent review and meta-analysis highlights the huge impact of fake and substandard drugs on health, trust in healthcare, and the economy

Around one in every eight essential medicines in lower income countries may be of low quality, or an outright fake. This was the conclusion of a review and met-analysis performed on relevant studies in five databases, including Pubmed and Embase, which allowed researchers to examine over 350 previous studies, which between them tested more than 4,000,000 drug samples.

"I recently transitioned to the School of Pharmacy at the University of North Carolina at Chapel Hill, where it struck me how important medicine quality is for protecting population health. Ensuring that medicine is doing what it's intended to do is critical to a trusted healthcare system. We wanted to know how large of a problem poor quality medicines is," says Sachiko Ozawa, first author of the review (1).

Substandard and fake drugs don't just fail to treat disease – they can prolong illness, and heighten the risk of treatment failure, poisoning and drug interactions. They can also contribute to antimicrobial resistance, posing a threat to the effectiveness of future treatments, explains Ozawa. "In addition, poor quality medicine can diminish people's trust in medicines, healthcare professionals, and the healthcare system itself," he adds, "and there are also economic impacts, from wasted resources and treatment of additional complications, to decreased economic productivity resulting from prolonged illness."

In a meta-analysis of studies that tested 50 samples or more, the researchers found that the overall prevalence of substandard and falsified medicines was 13.6 percent for antibiotics. Data on the estimated economic impact were limited and focused mainly on market size, but ranged from $10–200 billion – a substantial number for low and middle income countries, even by the conservative estimate.

The team is urging pharma to help. "The pharmaceutical industry has the technical know-how and screening technologies to detect substandard and falsified medicines. Greater collaboration and data sharing are needed to ensure that medicines are genuine, quality assured and trustworthy. Multi-stakeholder engagement of pharmaceutical companies with governments, international organizations, and experts are essential to ensure that medicines are safe and effective," says Ozawa. "We have an opportunity and obligation to tackle this problem, which threatens global health security and is essential to meet the United Nations Sustainable Development Goal to achieve universal access to safe and effective essential medicines."

Reference

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Injectable Innovation

A company looks to give the humble injection an inventive makeover with a new competition

What?

Contract Development and Manufacturing specialist Vetter recently launched a competition called the "Open Innovation Challenge – Injection 2.0" – and the winners have now been announced. Four teams submitted their best ideas to be in with a chance of winning a prize of €10,000.

Why?

"Vetter is always looking for new pathways that can help further develop the injection process," says Claudia Roth, Vice President of Innovation Management at Vetter. The core question of the competition was, how can can digital trends be used purposefully in regards to the application of injection systems?

"The goal of the challenge was to develop innovative, future-focused and sustainable ideas for the injection of medicines that are better streamlined to user needs than current methods," adds Roth.

Who?

Four multi-disciplinary teams (made up students, medical, economic professionals, and Vetter staff) participated in workshops and field-work. The initiative followed a user-centered method that involved direct communication with actual users of injection systems, including professional caregivers and patients. "The winning team developed a novel idea that has the potential to improve the documentation process as it pertains to the administration of drugs for healthcare professionals. This idea helps to make this process step easier, faster and safer," says Roth.

How?

"Choosing the winner was very difficult and required an engaged and intensive jury meeting; each of the four presentations was excellent," says Roth.

What's next?

The company will now decide which project ideas and elements to take further. Says Roth, "Through this activity, our company strives to promote and advance our innovation capabilities to significantly contribute to the preservation of quality of life for patients, both today and well into the future."

Partners in Success

Working with a CDMO is more than just gaining an extra pair of hands – a good CDMO is a true partner with advice on getting the most from your molecule.

By Nick Shackley

Today, many pharma companies are targeting niche therapeutic areas that require small API volumes. However, the APIs themselves are becoming increasingly more complex in terms of their molecular structure and often pose numerous challenges for formulators, such as poor solubility. A significant amount of work may be required to improve bioavailability and to develop a product that is truly efficacious in its function as it's formulated and delivered to patients.

Outsourcing is a very effective way for pharma companies to tap into additional formulation capacity and expertise. CDMOs will likely have experience with a broad variety of customers, regulators and difficult APIs, as well as specialized expertise in different approaches and techniques. Many CDMOs also offer different services and capabilities, allowing the pharma manufacturer to choose the right mix depending on the molecule they are working on, while avoiding the need to establish expertise in house.

Perfect partners

When looking for the right partner, pharma customers must examine how the CDMO's core technology development manufacturing capabilities align with the problem to be solved. It's also important to assess if the CDMO is capable of taking the molecule through clinical development with the lowest possible risk of delays. The hard assets of technology and capability are usually fairly straightforward to review – it's just a case of looking at the CDMO's facilities and expertise. But customers must also consider the human aspect of the partnership – and this can be far more difficult to analyze. Does the CDMO have good workers with the right skillsets? Does the overall culture of the CDMO match that of the customer, allowing the two parties to collaborate well together? And will the CDMO contribute to the project's success? A good CDMO is not just about doing what they are told – the best are also consultants and collaborators, with the ability to listen and give feedback and suggestions about the overall strategy and what approaches they feel are best for a molecule and its unique challenges. I believe that good transparency of the data and facts help to build a good, trustworthy relationship between the two parties.

Last but not least, I feel very strongly that the project manager is a key enabler in a successful outsourcing project. Even if you know a CDMO has the right assets and people, a project can easily fall apart if the execution is poor. All projects have their ups and downs – and many unexpected problems will need to be solved quickly and efficiently. A good project manager will help to keep the project moving and ensure that communication is strong throughout.

At Johnson Matthey, we have a global, cross-sector approach to project management and this is a function that we invest heavily in. It is a skillset no less important than scientific skills; after all, professional project management gives clarity to the customer and means that issues are discussed with the client promptly so that corrective action can be taken.

Adapting to needs

The pharma industry and its needs have changed substantially – and will continue to change in the future. Johnson Matthey continues to evolve to meet customer needs by investing in core R&D platforms, such as solid form sciences, chemical and bio catalysis, and continuous processing for API manufacture.

Around 11 percent of our workforce is involved in R&D and around 5 percent of our revenue goes into R&D technologies. We're aiming to have a full portfolio of R&D technologies that can service the full timeline of pharmaceutical development. I believe that all CDMOs need to think about the future if they want to continue to be successful – examining new technologies and understanding how they should best be deployed is a crucial part of that.

Interest in outsourced services is growing in the pharma industry given today's pressure on business. In particular, we are seeing strong demand for our offerings on how to determine the best solid form of entities and how to best engineer the solid form to make it both bioavailable and easy to manufacture at scale – the latter is something that is too often overlooked. Particle engineering, whether through standard approaches, such as milling, or more advanced engineering strategies, is also an area that is seeing increasing interest from customers. We are working hard in this area and investing in our equipment and capabilities to expand the number of options we can offer.

Nick Shackley is Global Vice President Innovator Products and Solutions at Johnson Matthey.

In My View

In this opinion section, experts from across the world share a single strongly held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of pharmaceutical development or manufacture. They can be up to 600 words in length and written in the first person.

Contact the editor at: stephanie.sutton @texerepublishing.com

Planning for Production Scale

The development of an industrial process should begin right at the start – when the product is still at the preclinical stage.

By Daniel Maier, Director of Engineering and Services at Zeta Biopharma, Germany.

The design and development of the optimal production process is a big challenge – and it's rare that upscaling runs smoothly. The growing demand of monoclonal antibodies (mAbs) requires efforts to increase production capacities and product titers. Experience shows that an ideal up-scaling process tends to rely on the field of hydrodynamics and process engineering; numerous indicators and values are needed to develop the right strategy. Many parameters, such as mixing time and the volumetric mass transfer coefficient (kLa), however, cannot be transferred in a linear manner, so successful up-scaling always involves compromises.

Mistakes made at the early planning stage can have a high impact later on. Insufficient agitator performance or inappropriate gassing rate and feeding strategy are common barriers that can affect productivity and cause product losses. Start ups, in particular, tend not to have the extra cash required to fix problems – but even large companies don't want to spend time and money fixing a process that should have been done right first time.

In recent years, I've been involved in workshops that aim to raise awareness of issues that need to be addressed in planning procedures. Process flow, functional specifications, architectural conditions or critical quality aspects need to be evaluated while considering all standards and regulations. It always fascinates me to see how companies are often completely unaware of the common, potential bottlenecks in their process steps and how these will affect their scale up! In my view, plant engineers need to be able to influence the planning process at a much earlier stage. Even at the preclinical stage, processes should be analyzed with a view to industrial-scale production and the conceptualization of a pilot plant. Right now, the whole industry is talking about fast-track projects, but these will only work out if plans are made in cooperation with those who build the plant. How can plant engineers give operational guarantees if they don't have the opportunity to influence the planning process?

"Plant engineers need to be able to influence the planning process at a much earlier stage."

The more precisely a process can be investigated and characterized at the early stages, the greater the chances of a smooth scale up. Today, there are plenty of tools that can be used to get a good view of what is happening during the process. For example, determination of concentration and temperature gradients via computational fluid dynamics (CFD) studies is a useful analysis tool for the prediction of process parameters. A precise determination of the kLa-value is a meaningful PAT tool as well, as it gives a comprehensive picture of what's going on inside the bioreactor. The kLa-value is also a suitable scaling indicator at the early stage: it allows for the calculation of oxygen uptake rate, as well as the estimation of the oxygen transfer rate via stoichiometric correlations in advance. Oxygen uptake and transfer rates represent a sound basis for the bioreactor and agitator design, and support the development of reliable scale-down models, where production conditions in commercial scale are simulated. The process optimization within the design space needs to be executed for each specific production system. As soon as any parameter changes, whether that be the expression system, media components or feed strategy, the performance indicators must be determined again to avoid product loss later on.

Investing in the right tools and expertise early on will pay dividends down the line. As well as optimizing the process, good engineers are also able to optimize the facility, through space-saving designs (easy to evaluate with 3D models) that offer easy access for maintenance and optimized interfaces between skids. A well thought out solution path along the entire planning process offers four key advantages: increased process safety, maximized productivity, reduced costs and shorter time to market.

Why Aren't We Connecting?

Digital technology is all around us, but pharma isn't quite getting it right… yet.

By Kal Patel, Senior Vice President of Digital Health for Flex, USA.

Healthcare today is largely disconnected, particularly when it comes to pharma's involvement. Only a tiny percentage of the potential information and relevant data that can be collected about patients is collected – and until pharma companies start collecting and harnessing this data, they will continue to live in a world of ignorance. As an example, consider this; a pharma company spends nearly $2 billion and takes over ten years to develop an innovative drug to treat an unmet medical need, which subsequently receives regulatory approval and reimbursement. The physician writes a prescription which passes through the system, but the only data that goes back to the practitioner, pharma company, or anybody else in the healthcare system, is whether the patient picked up their prescription. There is no information about whether the patient actually took the drug correctly and for the full term (unlikely), whether it worked, or whether it had side effects (with the exception of extreme cases). If more data could be collected, it would shed a lot of light on how the product and patient experience can be further improved, which should, in turn, improve patient adherence and outcomes.

In consumer industries, digital technology has created an immense feedback loop through connectivity that leads to iterative improvement in products and services, as well as personalization. In pharma and healthcare, the industry has been slow to lay the foundations to leverage real-world data that will drive iterative product improvement and customization. Starting with healthy consumers, pharma companies should be asking how they can use digital technology – perhaps through apps or wearable devices – that encourage people to make better lifestyle choices that improve health and potentially help fend off disease, or slow disease. For patients managing a disease, there is a tremendous amount of value in using digital technology to provide information about what really is happening at the individual patient level in real time. For example, a diabetes or COPD patient may see their doctor every three or six months to check their health status and adjust their medications, but

"The industry has been slow to lay the foundations to leverage real-world data."

"It should be possible to remotely monitor health and adjust the dosage continuously with technologies available today."

it should be possible to remotely monitor health and adjust the dosage continuously with technologies available today. This is an area that we are exploring with technology such as connected combination products integrated with smart algorithms.

I often compare pharma's digitization journey to that of the automotive industry. For starters, both have long product development cycles. The car industry takes about seven years from development to a brand new car coming to market. Similarly, it takes pharma companies about ten to fifteen years to develop a new drug. Secondly, both the pharma and car industries are extremely regulated because safety is on the line. Thirdly, the industries have both been dominated by large, established companies who have huge influence and control where resources are spent, both in the industry and in industries that support it.

The automotive industry began to "embrace" digital years ago, but this mainly equated to simple measures like adding a siloed GPS to new cars. However, introducing a new digital feature does not mean that the technology was implemented corrected. Surveys have shown that barely anyone uses the GPS that comes with their car for a variety of reasons – the biggest being that they were built with the same long product development lifecycle as the car and, hence, the user experience and interface were not only outdated and inferior, but did not go through the iterative product development that software products typically do.

In recent years, the automotive industry has upped its game. When buying a car, users would traditionally focus on raw horse power and the stereo system, but now it's all about the car's software – how it integrates with your mobile phone, music systems and more. In fact, when designing and building a car today, the investment has shifted from almost 100 percent hardware to around 50/50 hardware/software parity. The catalyst behind this transition from developing discrete products to connected systems has a lot to do with outside innovators that are disrupting the traditional automotive incumbents. The industry saw new models – such as Uber and Lyft – and new connected cars with growing autonomous features – such as Tesla and Alphabet's Waymo – and began investing in digital more seriously.

In my view, the same parallels exist for the pharma industry. The industry has put one foot into digital health by introducing incremental solutions such as using technology to improve patient enrolment in clinical trials, or by rolling out a companion app (most of which are very dull and are, in turn, not downloaded by patients). To succeed in deploying digital health solutions, pharma must think about how to do better. There are a few key principles that pharma companies can think about to accelerate their digital innovation efforts:

- Pharma has to embrace the concept of a minimal viable product and the fast-paced nature of technology innovation. Unlike traditional pharma product development, the first product – such as version 1.0 of an app – will be the worst version. But once you deploy an app, you can continue to rapidly improve it based on user engagement analytics and add more robust features.
- The industry needs to develop ecosystems as opposed to silos. Similar to the automotive example discussed earlier, patients will demand apps that integrate with connected devices and are contextualized with data about them and their lifestyles. In many cases, patients may be using drugs and devices from different companies for different conditions – do they really want an app for each one of these? Developing one-off solutions that don't integrate with other systems, such as electronic medical records, won't be successful.
- Companies should invest in developing truly unique digital health solutions, such as smart algorithms that can auto-titrate drugs or control connected medical devices to enable improved adherence or outcomes. We come across a lot of companies investing in building the underlying platform infrastructure to manage and analyze real-world data, but that's not where the true differentiation will stem from for a pharma company. Companies shouldn't be building infrastructure that will just create another silo (at best).

As with the automotive industry, we are seeing tech companies and startups begin to disrupt the pharma industry. The time is now for pharma companies to hit the accelerator in terms of their digital health efforts. There is too much at stake for patients and their shareholders not to move forward quickly.

Hear more from Kal Patel in Sitting Down With on page 50.

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For Bioprocess Success: Simulate!

How well do you really know your process? Modeling and simulation can reveal new information that can help you better prepare both your process and facility for the future.

By Emily Thompson

I've been using simulation techniques for almost 15 years in various areas, including scale up, technology transfer, and equipment design and coordination – and I passionately believe that the approach has many benefits. Right now, the pharma and biopharma industries are moving into the next generation of manufacturing. Many advances are hitting manufacturing both in terms of equipment and processes – consider the move to more cost-effective production and in some cases continuous manufacturing. And let's not forget the fast-moving world of cell and gene therapy, where many new companies are jumping into commercial manufacturing for the first time. Particularly when it comes to cell and gene therapies, many companies are struggling to select the best equipment and processes because they are pioneering new approaches. Often, questions about a project simply can't be answered with pen and paper, or an Excel spreadsheet – ultimately, you are just guessing. Modeling tools, however, can provide more accurate insight and ensure that you are designing your facility to work the way you want it to.

A process model is a computerized representation of a real world process and can be used to either reproduce the past for model validation purposes – or to predict the future. Models can be employed in a range of applications, including evaluating cost of goods, debottlenecking processes, planning clean-in-place, utility sizing, equipment selection, architectural planning, and even warehouse planning to support supply chain management. The beauty of modeling? It's highly customizable nature. You can use it for a high-level activity or intricate production details – and the findings are often fascinating. (For example, in warehousing, you'd be amazed how much time savings and congestion reduction can be made by simply evaluating the pathways chosen by forklift truck operators!)

Divination in practice

In biopharma, modeling is often used to quickly evaluate different production scenarios. When properly performed, a simulation can alleviate project unknowns and be used in tandem with traditional engineering design to efficiently design facilities suited for both current and future production. Notably, a process used today will not stay the same in the future – titers may increase, and there may be changes in technology. A model can be used to predict some of those changes and how they will affect support equipment. For example, a process today may have a titer of 5 g/L, but what if, in two or three years, this rises to 7 g/L or higher? If you need to make twice as much buffer, can your buffer handling operations cope as they are designed now? Or would it

"Design projects always go more smoothly when simulation has been used upfront."

be better to design the facility with flexibility so that changes can be made more easily in the future?

In my experience, design projects always go more smoothly when simulation has been used upfront. Today, many companies are keen to move from stainless steel to single use, but I often find that those companies don't have a great deal of data on how much single use is really going to cost. Single use may have a lower cost in terms of facility design and initial outlay, but the consumables cost is usually much more than companies expect. Here again, simulation can help by setting out exactly what the consumables cost will be, allowing a company to examine all the different ancillary pieces that they may not have thought about at first. When moving from a stainless-steel vessel to a single-use mixer, it's clear that you will need single-use bags, but companies can overlook all of the tubing needed to connect the single-use mixer to other pieces of equipment. Modeling and simulation can reveal that information upfront, giving you more data on which to base your decision – rather than just finding out after you've made the switch. In one facility design project I worked on, the client was keen to have a primarily single-use facility, but once cost-of-goods modeling was performed and the data presented to the client, stainless steel proved to be the more economical long-term solution given their planned production rate and scale. The resulting data caused a complete change in design, showcasing the true value of simulation: its ability to drive a project forward in the best direction.

I've also used modeling for clean-in-place debottlenecking in a stainless steel facility. We had to model the pathways of flow in incredible detail, including going right down to individual valves. This couldn't have been done without simulation software.

The model maker

Before building a model you need to know what you want to achieve. Too often, I've seen companies with a "fuzzy" picture who plan to build a model and "see what comes out of it". If you don't know what you want your model to do, you won't be able to collect the right data – and to make a good model, good data is paramount. The better your data, the better your model! Getting the right data is usually the biggest challenge in making a model and will involve walking about the facility, talking to operators and examining batch records. The models I have worked with have been very accurate when it comes to comparisons against real production data. There will always be variables in real world production, but a good model should give you a good understanding and appreciation of the overall feel of the facility and what throughput is going to be like. As the model evolves, however, you may find new areas to explore as the model brings information to light about production processes.

There are dozens of commercially available simulation and modeling tools on the market – each has their own pros and cons and application areas. I advise using a specific software platform that is best suited for the intended application – don't just assume you can perform production debottlenecking and cost of goods analysis with the same software tool! Once you have the data, you should typically build the model as the facility is currently functioning. If the model is able to mimic the process correctly, you know it works and you're ready to run "what if" scenarios.

One final piece of advice: when embarking on your modeling journey, it is very important to remove bias. Some people distrust models or believe that they know their own processes so well that there is no need for them. But modeling can often bring to light bottlenecks or room for improvement that were not even on the radar. In many cases, particularly with cost-of-good models, people have assumptions upfront about what would be cheaper, and so use these biases to influence the data entered into the model. Other times, people may not use the model effectively or only run a single brief simulation. With modeling, you must be objective. Choose the right software, collect the right data, and be thorough with your simulations. Leave your biases at the door and let the data speak for itself!

Emily Thompson is a Process Engineer at CRB.


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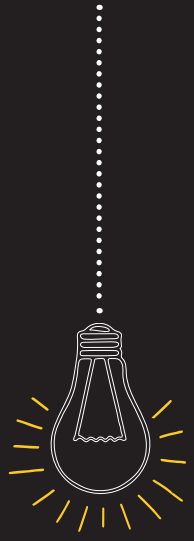
TIME FOR PHARMA TO DELIVER?



For the vast majority of pharmaceutical products, data on safety for pregnant and lactating women and their fetuses and babies is not available. But going without essential medication is not the right solution – failing to treat health conditions could lead to equal or increased risk for mother and child. Here, we seek the path to a more enlightened approach.

BY ROISIN MCGUIGAN

The adequate inclusion of women in clinical trials is an issue with an increasing level of awareness – and it's a topic The Medicine Maker has covered previously (1, 2). But there is one particular group of women who continue to be far more underserved by clinical research: pregnant women.

And there's a good reason the problem should not be ignored: according to the FDA, half of pregnant women report taking at least one medicine (3). Worrying then that, of the 172 drugs approved by the FDA between 2000 and 2010, 97 percent had an "undetermined" risk for pregnancy. Perhaps worse, for 73 percent of new drugs the amount of data available on safety in pregnancy was rated as "none" (4). Every day, pregnant women need to make decisions and balance the risks to their own and their unborn children's health when deciding to take – or not to take – medications for which no clear guidance is available. Often, the health care professionals advising them can't offer much help either, for the same reason: the data they need simply doesn't exist.

I spoke to doctors, researchers, and those within the pharma industry to understand the depth of the problem – and how it should and could be addressed.

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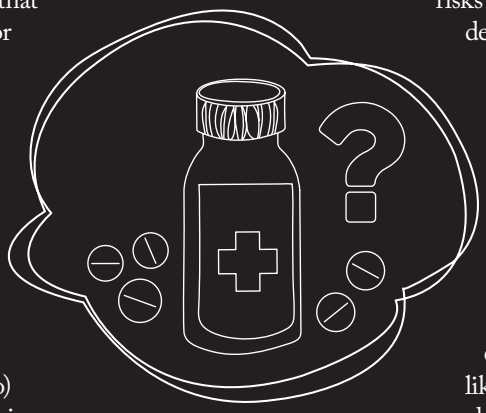
Pregnant Patients Deserve Better

BY ANNE DRAPKIN LYERLY, MD, PROFESSOR, DEPARTMENT OF SOCIAL MEDICINE; RESEARCH PROFESSOR, DEPARTMENT OF OBSTETRICS/GYNECOLOGY; ASSOCIATE DIRECTOR, CENTER FOR BIOETHICS, UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL, USA.

In my view, the pharma industry is not yet doing enough to address the lack of prescribing information available for pregnant women – but right now, none of us are. Unfortunately, there are important disincentives. Some of them are economic, but there are regulatory and ethical complexities as well. Caution is often preached when it comes to pregnant women and research, but I think it is important to think about the ways that caution has been distributed – unevenly and unfairly. Of course testing medicines and prescribing them in pregnancy is an area that requires care and caution, given the risks that some of these medications might entail for women and their offspring. But much less attention has been paid to the risks of not testing or prescribing, and those risks can be significant.



The unwillingness to test medications has led to a dearth of data to guide dosing or give providers information about the safety profile of medication, and can make them reticent to use medications important for maternal or fetal health. Often providers making prescribing decisions (and women too) think that by not prescribing (or taking) medicine they are being "better safe than sorry." But failure to treat illness can have dire consequences: in pregnancy, untreated depression is associated with fetal growth restriction and prematurity, even suicide; untreated asthma is associated with preeclampsia, premature delivery, hemorrhage and low birthweight; in women with diabetes, inadequate glucose control can result in a high chance of severe birth defects; failure to continue treatment for multiple sclerosis in pregnancy can leave women permanently unable to walk. When essential medication is avoided, the risks to women and their children can be huge.

As a physician, I often felt frustrated about not being able to provide the data or reassurance my pregnant patients need and deserve when it comes to the medicines they take – and that frustration has profoundly shaped my career. My medical training is in obstetrics and gynecology, and I was particularly drawn to the field because of the complex social and ethical issues involved in treating pregnant women. As I took care of patients and encountered these myriad issues, I found that there was not much in the literature to help me navigate them. It occurred to me that there was a big gap – and a significant need – for a conversation around these issues that was steeped in both clinical and scientific expertise, as well as robust social and ethical methods and theory. I did a fellowship in bioethics, and from then on my approach has always been at the intersection of ethics and women's health. And it is an intersection that still requires a tremendous amount of work.

As I identified pressing questions facing women's health, and worked to address them, my passion only grew. And as a physician caring for women, I found the lack of evidence to guide care not only frustrating but also, to be frank, ethically unacceptable. I would have a patient who needed a medication to stay healthy during pregnancy but could offer only experience and intuition to assure her that the drug I was prescribing was safe and effective in her changing body – but I could not offer her scientific evidence. I could emphasize what we knew about the harms of not taking any medication (which tend to be greater than the risks of taking them), but I knew my patients deserved better.

A question of ethics

As I learned more, I was also concerned about the way that people were construing what ethics required. I have served on several research oversight committees (Institutional Review Boards, or IRBs) over the years. Most studies that we reviewed excluded pregnant women, even studies that didn't impose any risk, like interview studies. No wonder there was no data on drugs in pregnancy! Nobody on the IRBs talked about whether this was appropriate or fair.

When I raised the question of whether it was right to exclude pregnant women, I didn't get much traction. Some IRB members thought it was outside the scope of the IRBs authority – offering that their primary purpose was to protect people from the harms of research rather than make sure there was fair access to its benefits. Others suggested that it would be too ethically complex – or unethical altogether – to expose pregnant women to the risks of research.

I realized that we needed clarity on the requirements of ethics, and so I partnered with two colleagues in bioethics – Maggie Little at Georgetown, and Ruth Faden at Johns Hopkins. We published a paper that explained the ways in which exclusion of pregnant women was ethically problematic (1). We argued that ethics doesn't preclude their inclusion in research; rather, ethics requires it! And from there the Second Wave Initiative – a research and advocacy effort to ensure that the health needs of pregnant women are fairly addressed in the biomedical research agenda – was launched.

"I found the lack of evidence to guide care not only frustrating but also, to be frank, ethically unacceptable."

Bringing pregnant women into the picture

Our initial goal was to make vivid the ways in which the status quo – that pregnant women and their interests were excluded from most research – was ethically unacceptable. We laid out the reasons in our paper and in several other articles in the literature, as well as raising the subject in the media. When issues arose that highlighted the problems of exclusion, we wrote about them too.

For instance, as the H1N1 epidemic hit and disproportionately affected pregnant women in 2009, we wrote in the New York Times about the ways in which the absence of data for anti-influenza medications may have made matters worse (2). Later that year, we wrote a longer piece in the Times about the ways that the lack of evidence harmed women in the context of H1N1, and the importance of gathering the needed evidence (3). We also pointed out opportunities to collect what we called "low hanging fruit": data that could be gathered without imposing any risk on women or solving any difficult ethical puzzles. One example was a piece we wrote in the American Journal of Public Health about the National Children's Study, a large US study that planned to collect data on the effects of the environment on 100,000 children – at least 90,000 of which would be enrolled before birth (4). In other words, this was a huge study that enrolled pregnant women. But as designed, maternal health indicators were collected only as predictors of children's health. In short, the study enrolled pregnant women but studied them as part of a child's "environment" rather than as ends in themselves.

Clearly, we need to get pregnant women, and their health interests, back into view. It seems like the Second Wave Initiative is taking hold, and a conversation about the evidence gaps around pregnant women and the harms that ensue is developing. For instance, this year we will have a report from PRGLAC, the NIH task force established by the 21st Century Cures Act to advise the secretary of Health and Human Services (HHS) on gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women (see "A Tall Task"). In addition, the FDA recently asked for feedback on draft guidance for research with pregnant women. In that document, they described the need to fill research gaps for drugs and biologics in pregnancy as a "critical public health need" – an important and powerful statement from the FDA. And it is also absolutely true. We simply cannot afford to continue to leave pregnant women out of conversations about public health.

Right now, my research group is working hard on what we call the PHASES Project (www.hivpregnancyethics.org). It is an NIH-funded project that I have been leading addressing ethical challenges to filling research gaps around pregnancy and HIV and it comorbidities. We have done extensive research and stakeholder engagement, including a qualitative study of 140 women in the US and Malawi that explored their views and experiences about HIV research and pregnancy, as well as interviews with a range of individuals who help shape the HIV research landscape, including researchers, scientists, policymakers, IRB members and other experts in the US and Southern Africa, and are in the process of publishing our findings (5). We have convened a Working Group of truly outstanding leaders in HIV and women's health that is charged with developing ethics guidance for HIV research in pregnancy, which we hope to launch later this year.

Exclusion brings its own risks

As for my advice to pharma: it is important for any entity conducting research to consider pregnant women and their interests in their product development plans. For instance, for drugs likely to be used by pregnant women, reprotoxicity studies should be conducted earlier – ideally before large scale efficacy trials are underway. Pharmacokinetic studies should also be conducted where drugs are likely to be used in pregnant women. Often these studies can be done "opportunistically" meaning the research-specific risks are minimal and limited to the risks of a blood draw.

I would urge the pharma industry to be mindful of the risks of not conducting these trials. You only need look to the recent events around the HIV medication, Dolutegravir. After it was widely distributed, a prospective study suggested an increased risk of neural tube defects among children whose mothers took the drug around the time of conception (these findings are preliminary, and further data are needed to confirm or refute them) (6). Such information is absolutely critical to helping patients make informed decisions about which medications to take, and also about contraception and pregnancy. Some people may worry that findings like this – that may or may not be clinically significant – could interfere with development of potentially beneficial drugs. But as obstetricians and others are very aware, few decisions, including the decision not to take a medication, are risk-free. Clearer data on the risks and benefits of drugs to pregnant women will help us all identify

the best ratio of benefit versus risk, allowing us to optimize care for both women and their children.

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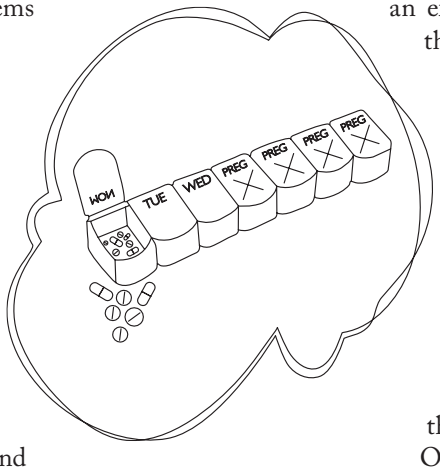
A Pharma Success Story

BY ÉRIC GERVAIS, EXECUTIVE VICE-PRESIDENT, DUCHESNAY, CANADA

Duchesnay's focus on maternal health stems from personal experience. We are a family-owned company and, back in the 1980s, a member of the owner's family experienced an issue with her pregnancy. She discovered that the information provided by her physician and her pharmacist was very different – her physician thought that a drug was safe to use, but when she went to obtain the drug she discovered that her pharmacist was unwilling to dispense it, as they felt there was a lack of information available to show the drug was safe in pregnancy. Ultimately, she found that the decision on whether or not to take the drug was down to her alone. The family felt that this was a lot of responsibility to place on individual pregnant women, and so the decision was made to transition away from the former focus on over the counter drugs in favor of a new mission: to become a pharmaceutical company that could provide reliable medical information and medications to women and their unborn children.



We consider ourselves pioneers in this domain. A limited number of other companies are developing drugs for use during childbirth, but developing drugs for use during pregnancy remains a challenge and there are no other companies doing quite what we do. There are many issues to consider, including the fact that regulatory agencies in different countries don't have a lot of experience in this space, as there are so few companies developing drugs for pregnancy. There are ethical issues, as you need to ensure you are not putting pregnant women at risk. And don't forget the legal issues: you don't want to put yourself at risk either. The lack of existing data is also a problem. Regulatory agencies aren't even sure what to ask you – or what research you should be doing to prove your drug is safe! The area is so new that everything you do, you have to figure out by yourself. You can't simply look to what other companies have done, or seek advice and guidance from regulators. Nevertheless, here at Duchesnay, we decided to take on these challenges… And it has paid off.

Successfully sailing uncharted waters

Studying pregnant women isn't the most straightforward of tasks, but personally, I think the biggest issue isn't that pharma companies don't want to do more – it's that regulators and governments need to step in and help them. For example, in the US, Congress passed the Pediatric Research Equity Act in 2003, which provided pharma companies with an extension of marketing exclusivity when they carried out pediatric trials – providing a financial and regulatory incentive to do the work. If governments could do the same for pregnant women, it would encourage pharma to tackle this tricky area. Pharma companies know how to do research, but it is very complicated to develop drugs for pregnant women – a great deal of resilience is required as it takes so many years of research to get a treatment that is safe and effective. Time and resources are expensive, and so the process needs to be financially viable.

On the other hand, where there is a will, there is a way – and Duchesnay is living proof of that. Whether we study pregnant women or not, they will be exposed to many different drugs. You don't stop being sick when you get pregnant – if you have a chronic disease, it won't magically disappear when you conceive, and it's not as simple as

> "The area is so new that everything you do, you have to figure out by yourself."

just stopping your medication either. It's incredible to consider the amount of drugs that pregnant women are taking every day without proper research. There's so much we still don't know, but the information is out there – women are making these medication decisions every day, and that represents a wealth of data we could be collecting and using to help women make more informed decisions.

When Duchesnay first moved into this field, I think it's safe to say that we didn't know quite what we were getting into. We had to turn to specialists – teratology and mother and baby expert groups, the NIH and so on – to understand what we needed to do and how we should provide data to gain approval. Where we are today represents years and years of research and hard work – but being able to develop drugs to help women has been hugely rewarding.

Making a real difference

I believe our nausea and sickness drugs, marketed in the US and Canada, are having a huge impact on women's lives. It's a common misconception that morning sickness during pregnancy is normal and benign. For some women it is very severe – and there is also the more extreme version known as hyperemesis gravidarum to consider. It can be so debilitating that women might need to be hospitalized, and may even feel unable to continue with their pregnancy. Having access to a drug that can treat the condition allows women to continue with their pregnancies – and even give them the confidence to go on to have another child. It's incredibly gratifying to know that our work is able to change women's lives.

We exist in a niche market in terms of competition – but the unmet need is gigantic. If you want to develop a treatment for depression or diabetes, the competition is fierce. But if you are offering a diabetes or depression treatment for all the pregnant women suffering from these chronic conditions who aren't sure which treatments are safe to take, it's a very different story. The potential rewards of being able to offer something proven to be safe are significant. And the possibilities are almost endless; there is so much work still to be done, so I'm certain that pharma companies who choose to embrace the same mission would see a return on investment with perseverance.

Taking the Initiative

Not all regulators and pharma companies are avoiding the issue of pregnancy and drug development – the FDA has recently released draft guidance for industry on the ethical considerations for inclusion of pregnant women in clinical trials (1). The finalized guidance will aim to provide the FDA's recommendations on how and when to best include pregnant women in trials for the development of drugs and biological products.

"This is specific advice for industry, which aims to highlight both scientific and ethical considerations and provide guidance for both the premarket and postmarket settings. It looks at both considerations for women who are pregnant, and those who become pregnant during clinical trials," says Catherine Spong. "Importantly, it is currently in draft form – the FDA are keen to receive comments to understand if there are aspects that people would like to see changed." Once finalized, the guidance should offer drug developers a better understanding of how to approach pregnancy in clinical trials and how to provide this information to the FDA.

On the other side of the table, some pharma companies are taking the initiative to better understand how existing drugs affect pregnant women: the GSK pregnancy registry is a series of observational studies tracking the effects of a number of prescription medications and vaccines on pregnancy outcomes in consultation with the CDC (1). The studies aim to record outcomes in women who have been exposed to the drugs at any time during their pregnancy – and interim results have been made available to assist in toxicology studies and to allow clinicians access to information that may be relevant to their patients.

"As social awareness of this issue increases, I think it presents a unique opportunity for us to be able to pull together industry, regulators, physicians, scientists, and patients and their advocates to really address these outstanding questions and provide the best information we can on how to move forward with drug development in these populations," adds Spong.

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"Whether we study pregnant women or not, they will be exposed to many different drugs."

I personally believe that most existing drugs must be fairly safe during pregnancy. Around 50 percent of pregnancies are unplanned, so if every single drug a women might be taking when she finds herself unexpectedly pregnant was teratogenic, the rates of birth defects would be far higher than what we see in reality. But clearly, that's not enough. Access to comprehensive information that allows informed decision-making is every pregnant woman's right. It's time we all put our shoulders to the wheel – governments, industry, and advocacy groups – to make sure women don't have to spend any longer in the dark about their medication choices.

Including Pregnant Women from the Start

BY CATHERINE SPONG, PROFESSOR AND VICE CHAIR, OBSTETRICS AND GYNECOLOGY; DIVISION CHIEF, MATERNAL-FETAL MEDICINE, UT SOUTHWESTERN MEDICAL CENTER, DALLAS, TEXAS AND FORMER CHAIR OF PRGLAC

During my time as chair of the PRGLAC task force, I worked with and spoke to industry representatives and those in the private sector about the barriers to gathering data on medicines in pregnancy. One of the key things I kept hearing (something that we as clinicians are very aware of) is that it's very uncommon for there to be medications that are specially tested in pregnant women. And for lactating women the problem is doubled, with incredibly limited information. And yet, we routinely prescribe medications during pregnancy and lactation. It's a complex area: on one side, people say, "You should not test in pregnant or lactating women because of the potential risks and liability." But you hear a similar argument on the other side – "in pregnancy, it's very important to know what would be appropriate to take and what to avoid, because of the developing fetus."

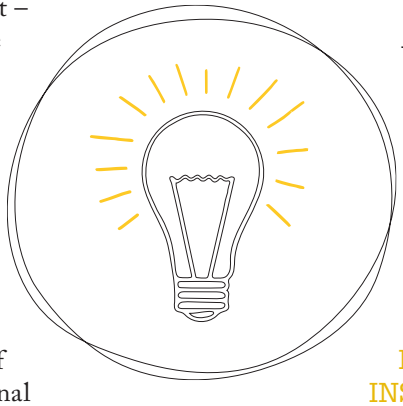
"If a medication is approved for women of reproductive age for a condition that continues in pregnancy – such as hypertension or asthma – it is being used on-label."

The reality, in the US at least, is that if a medication is approved for women of reproductive age for a condition that continues in pregnancy – such as hypertension or asthma – it is being used on-label, as described by representatives from the FDA at the PRGLAC meetings. But we have limited or no dosing recommendations and limited data, even though we know that a women's physiology during pregnancy and lactation is different – blood volume doubles, there's change to the binding proteins in the blood, GI transit time is different, as are kidney and liver function… and all of these changes could affect how a drug is bound, processed or cleared by the body.

In essence, when a new drug is being developed, if the drug is aimed at women of reproductive age then it is likely to be used by pregnant women whether intended or not. For example, if a new drug is being developed for seasonal allergies, it would not be surprising if some women got pregnant while taking the medication. This should be considered when designing the study – to include following women who have become pregnant or who are lactating. Having more information about what dosing changes may need to be made for pregnant women, or if there are any safety concerns for women who become pregnant, would be beneficial, including for healthcare providers seeking to advise patients, and the women themselves.

I have been involved in many clinical studies involving pregnant women – and it's not as difficult as some might think. There is an ongoing maternal/fetal medicine unit network of sites across the US that performs clinical trials and studies in high risk and normal pregnancies, trying to optimize outcomes. These include randomized controlled trials, observational studies, and therapeutic interventions; one example was a trial of thyroxine in the setting of subclinical hypothyroidism. The important aspects are to ensure that the women enrolled in the trial understand why the trial is being done, what their participation means, and providing staff who can answer their questions and facilitate their participation in the trial, if they are interested.

My advice is to evaluate each trial and study and start with consideration of inclusion. It is important to scrutinize *why* women are excluded when the study is initially designed and determine if they truly must be excluded and, if so, why? Not to simply assume from the outset that exclusion is the best course of action. I'd like to see us move towards a mindset where we begin with the assumption that pregnant and lactating women should be included in studies and trials, unless their removal can be fully justified. Pregnant women shouldn't be an afterthought – we need to build their needs in from the beginning of drug and therapy development.



A Tall Task

FROM AN INTERVIEW WITH DIANA W. BIANCHI, M.D., CHAIR, TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT WOMEN AND LACTATING WOMEN; DIRECTOR, EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT, NATIONAL INSTITUTES OF HEALTH, USA

The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) was mandated in 2016 by the 21st Century Cures Act (1). PRGLAC was charged with providing advice and guidance to the Secretary of Health and Human Services (HHS) on activities related to identifying and addressing gaps in knowledge and research on safe and effective therapies for pregnant and lactating women. In other words, what can researchers, health care providers, and medical professionals do to ensure that pregnant women and nursing mothers receive appropriate doses of medications?

"More than six million women are pregnant in the United States each year, and it is estimated that more than 90 percent of them take at least one medication during pregnancy and lactation."

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) led a series of Task Force meetings in 2017 and 2018, working with stakeholders from industry, government, and academia. A central theme resonated throughout these meetings: the need to alter widespread assumptions that have significantly limited scientific knowledge of therapies used by pregnant and lactating women. Currently, pregnant and lactating women and their healthcare providers are left with undesirable options: either taking a therapy without high-quality dosing information or not treating a condition. In the case of lactation, women may be choosing to discontinue breastfeeding to take a therapy based on limited information, which then deprives the mother and infant of the benefits of nursing.

More than six million women are pregnant in the United States each year, and it is estimated that more than 90 percent of them take at least one medication during pregnancy and lactation. However, these women often are excluded from clinical research that could help them, even though many therapies are already used by pregnant and lactating women and are necessary for their health. Without research to establish an evidence base, health practitioners need to make decisions with limited information on appropriate dosing. Indeed, a cultural shift is needed; the importance and public health significance of enhancing research efforts to inform medical decision-making for pregnant and lactating women must be recognized.

In September 2018, the Task Force submitted a report with 15 recommendations to HHS Secretary Alex Azar and to members of Congress. Some of the recommendations include removing regulatory and legal barriers preventing research, increasing public awareness of the need for better research in pregnant and lactating women, and providing financial incentives and support to facilitate research and public/private partnerships (2).

Learning about pregnancy medications from the source

NICHD also leads PregSource, a crowdsourcing research project that aims to gather information about pregnancy directly from pregnant women. The project aims to learn about the experiences and health of pregnant women and, eventually, their babies – information that promises to inform future research strategies and improvements in maternal and infant care. We've recently added a medication tracker to PregSource so that participants can share what medications they are taking to help researchers gain a better understanding of the range of therapies used by pregnant women and nursing mothers.

Taken together, initiatives like PRGLAC and PregSource will hopefully start to change the way we approach the use of therapies during pregnancy and lactation. The more we see industry and academia designing studies that include pregnant and lactating women, the better.

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Dissecting How Drugs Work

Frank Fischer and Sven Poetzsch have a shared goal at Merck: to understand how medicines interact with human biology. In this pursuit, cutting-edge omics research is key.

Sven Poetzsch is Scientific Manager – Strategic Operations Bioanalytics and Biomarkers, and Frank Fischer is Laboratory Manager – Biomolecule Analytics, both at Merck.

How do the omics fit into drug development?

Frank Fischer: The central driver of the omics concept is to achieve a deeper understanding of the biology of diseases. In very simple terms, we are looking for different patterns and the integration of information to build a better profile of a disease, and to understand what happens when it is treated. How does the medicine work? Does it have side effects? If so, how can we minimize these side effects? Many drugs end up failing clinical studies because severe side effects were not recognized in the early stages. The more you know about a molecule early on, the more you can be prepared for the future, and the better opportunity you have to optimize the treatment in the right direction – this is especially important in personalized medicine.

Sven Poetzsch: Omics technologies give us the ability to better understand what is happening on a molecular basis and should result in more targeted treatments. In addition to the aspects mentioned by Frank, such knowledge could also, in time, streamline processes and reduce the number of studies, while increasing the success rate for our drugs. A deeper understanding of the biology of the disease could also enable us to identify new targets and treatment approaches.

What are your roles at Merck?

FF: In my lab, located in Site Management Analytics and thereby supporting a variety of different topics within Merck, we focus on the characterization and identification of proteins and proteomes. For example, we will examine the protein sequences and check for post-translational modifications. We also do a lot of work with proteomics by setting up technologies to better understand the effects and selectivity of our compounds and how they affect the living cell. We use a range of different technologies to detect and identify protein-compound interactions within the cell, as well as try to estimate side effects.

SP: At the beginning of the year, I took on a new role within Site Management Analytics which deals with strategic topics in the context of healthcare analytics and omics technologies. We mainly deal with the quantification of compounds in biological matrices. In short, we want to know what our compounds do inside the body, and what our bodies do to the compounds! We work with cells and animal models and then, later, with samples from patients in the clinic. For a compound to be efficacious, it needs to be absorbed and distributed in the body. All compounds that enter our bodies will also eventually leave so the compound will also be metabolized and excreted. To optimize compounds in the context of efficacy and safety, it's really important to understand exactly what happens, from the compound entering the body to leaving.

We also look for metabolic biomarkers, which is where omics technologies come in. In this context, a metabolic biomarker categorizes the effect that a drug has on the body and can be a quantitative measure of an effect, how well we hit our target, and how well suited the drug is to the pathway we are targeting. Metabolic biomarkers can be also used as safety measures to identify toxic or unwanted effects; and the same applies for protein biomarkers.

How do your teams work together?

FF: What unites us, of course, is that we both want to gain a better understanding of what really happens on the cellular scale when somebody takes a medicine! We both have slightly different focus areas, but there is often overlap. I mainly focus on qualitative and semi quantitative protein analysis, such as elucidating the structure of proteins and tracking protein-compound interactions. Meanwhile, Sven

> *"We both want to gain a better understanding of what really happens on the cellular scale when somebody takes a medicine."*

focuses on small molecules and does a lot of work with metabolomics. When it comes to absolute quantification of proteins, our technologies will overlap. For example, if a partner asks how much of the protein is within the cell then there is a connection to Sven's former lab.

SP: Mass spectrometry (MS) is a key technique for both of us. We use HPLC coupled to MS systems in different ways. Frank normally uses high resolution MS for his applications, and in my lab we use mainly tandem MS to quantify compounds. One of the obvious overlaps is that it is sometimes more beneficial with the machines in my lab to quantify compounds or even signature peptides as surrogates for the target protein.

We also collaborate on the characterization of antibody drug conjugates, where there is a combination of monoclonal antibodies that target cancer cells and cytotoxic payloads. So Frank will look into the identification and structural characterization of proteins, and I will take care of characterizing the small molecule related components, such as linkers and toxins.

What technology developments have been most important for your work?

FF: For me, it's mainly a new technology that we implemented last year called cellular thermal shift assay-mass spectrometry (CETSA-MS®), which enables hypothesis-free identification of drug to protein interactions inside the cellular environment without the use of labels. Label-free analysis is important because labels can sometimes influence the interaction of the compound and the protein. The CETSA-MS® technology also allows for off target detection, which means that we also gain important information on potential side effects.

SP: In the field of quantitative bioanalytics, the changes have not been quite as tremendous as in the world of protein analysis. There have been improvements with regards to sensitivity and speed, but overall the general concepts have not changed significantly over the past few years. In the future, I'd like to see more developments based on high-resolution MS and combined qualification/quantification strategies.

In the omics field, there is a close link to data sciences. Traditionally, science was all about a single experiment, but more and more we need to analyze a huge amount of samples in a processed way. And as we work with complex systems, you really need more than one technique to tackle the challenges. Perhaps you'll start with genomics and delve into the transcriptome, then go to the proteome, which will have an effect on the metabolites you find in your samples or in the metabolic system of cells or the body. The systems that we use in the proteomics and the metabolomics field are really powerful and create a huge amount of data, but for this to be useful we need to get the right answers out of that data and turn it into useful knowledge. Bioinformatic approaches are highly important; perhaps in the not-too-distant future we'll see great progress by artificial intelligence being applied to make sense out of increasing amounts of data.

What makes your field so exciting?

FF: When using omics technologies you always see something unexpected. And then you ask yourself: why? This ongoing puzzle is a huge inspiration and part of the reason I love the field – the new insights offered by omics always drive me to understand things further. I am also very excited about the potential for personalized medicine. The mapping of the human genome has opened up intense studies in proteomics, metabolomics and transcriptomics, and we are gaining a much deeper insight into individual differences between patients. We've always known that some drugs work better in some patients – in men, or women, or different ethnic groups – but now we are learning why. We may be able to translate this knowledge into tailor-made treatments – perhaps combination therapies – that have a higher probability of working for key patient groups.

SP: For the most part, our insight into biology is still patchy, and the fact there is still so much more to uncover makes it a very exciting field to work in. Even if you spent one hundred years in the omics field I think you'd still be discovering new things. Mass spectrometry allows us to see much deeper into biological machinery and understand some of its complexities. Ultimately, this is all about helping patients and I'm convinced that understanding biology on a molecular scale will lead to better medicines and treatment options.

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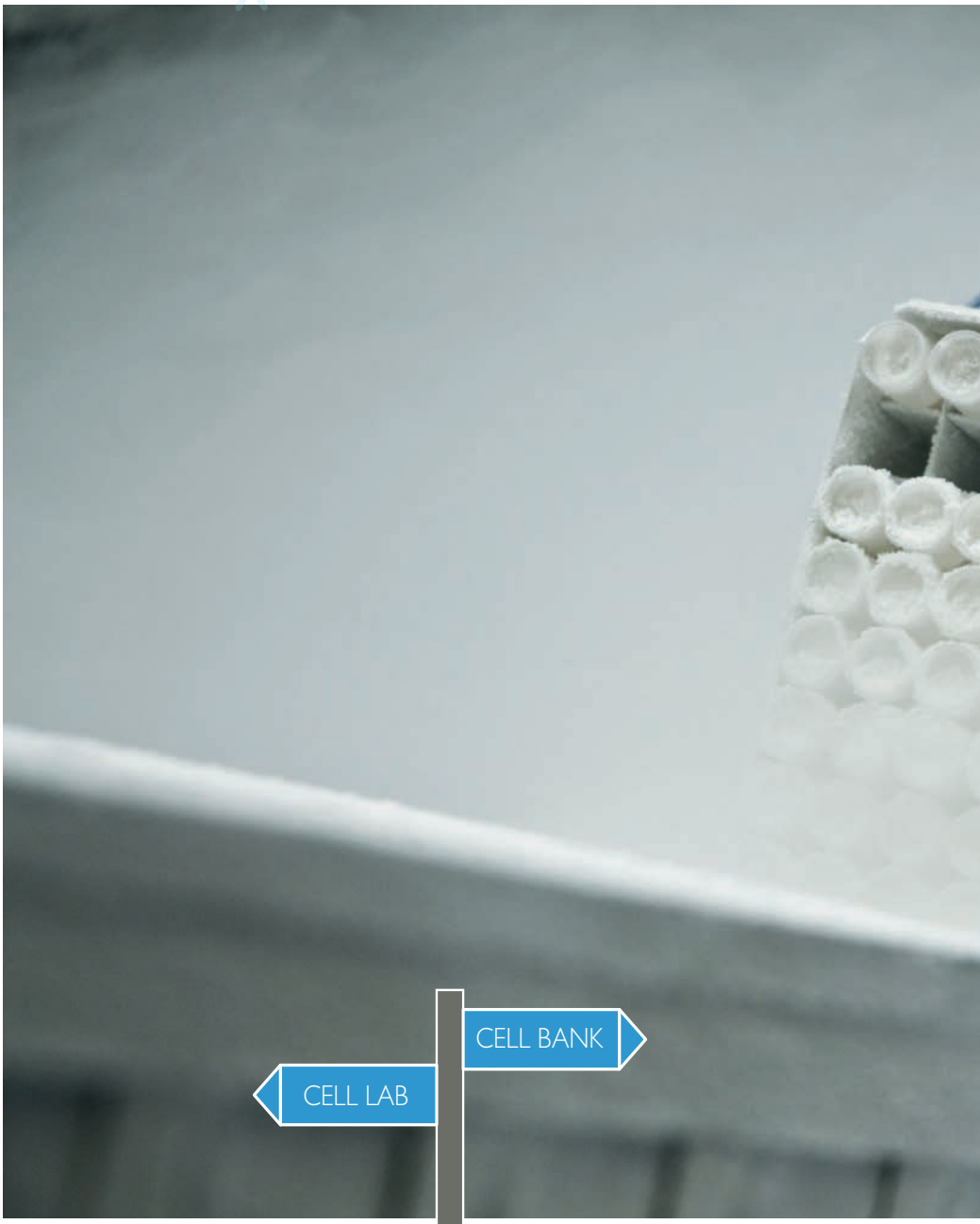
Banking for Bioassays

Analytical bioassay cell banks certainly have benefits. But with little guidance on how to get them up and running, it can be difficult to know what best practices to follow.

By Mike Merges and Mike Sadick



As technology advances, regulators are demanding ever-greater precision, accuracy and reproducibility of assays used during pharmaceutical development. The goal is clear: to ensure that the products ultimately delivered to patients are of high quality. Bioassays are an important component in ensuring regulatory compliance, and effective bioassays require reproducible cell lines; analytical bioassay cell banks are commonly used to provide the necessary cells.

There is a large amount of guidance – both regulations and standards – governing the production of GMP production cell banks, notably the ICH document Q5D on the derivation and characterization of cell substrates used for production of biotechnological and biological products (1). These will be serially sub-cultivated cells that are characterized by common starting sources for each production lot; in other words, they are preserved banks of cells. The guidance states that the identity, purity and stability of the parental cell line, and subsequent master and working cell banks, must be confirmed.

For analytical cell banks, however, the situation is not so clear-cut. In fact, there is no real guidance on what is required. Perhaps the best current set of recommendations is contained in a 2012 paper by Menendez et al., which also states that non-GLP and non-GMP best practices should be performed and documented in a way that it is consistent with the future use of cells in analytical methods that have to comply with GLP or GMP (2).

Several factors should be considered when making an analytical cell bank. In many cases, it is appropriate to use a tiered banking strategy, with master and working analytical cell banks. The cells can be frozen in appropriate media for future

"Stable and predictable cells are essential for running accurate and reproducible bioassays."

use. There are numerous technologies available to control the freezing of cell banks, but the cells must also be subject to analysis performed under protocol, to check both their purity and their function. A purity analysis involves two-stage viability testing: immediately after the thaw, and again a day or so later, including tests for fungal and bacterial sterility, as well as mycoplasma testing. For assay function, at least three random vials from each master and working cell bank should be tested in the bioassay itself.

The most important advice that we can give is that you must develop a good understanding of the cells, culture reagents, and conditions, and ensure that the cell bank is appropriate to support your bioassay. As a non-GxP procedure that will support GxP analysis, a quality assurance signature may still be required on protocols and reports, with substantial documentation for every step. You also need to bear in mind that the biology of cells is variable. Naturally, any plate-based assay may show variability during development and use – variability that can be exacerbated if your cells are not reproducible. You'll also require proper procedures and documentation to ensure that the characteristics of the cells themselves are known.

Putting cells to the test

The history behind your cells and cultures can significantly affect the phenotype of the cells, and therefore their morphology and response. Because of this, it is important to maintain a full history of your cells to ensure their provenance, including the tissue type, method of isolation and type of cell. There should also be good documentation of the passage or population doubling history, the media that have been used for culture, and

"The most important advice that we can give is that you must develop a good understanding of the cells, culture reagents, and conditions."

any prior results from cell identity and biological quality tests.

ICH Q5D for production cells states that appropriate tests should be performed to determine that the banked cell is what it is claimed to be, including its phenotypic and genotypic characteristics. It is not necessary to carry out every single possible test, but several should certainly be done to guarantee that the cell is what you think it is.

Examining the cells' form and structure with photomicroscopy is one test that can be performed, but it can be tricky, and is usually only viable with adherent cells. Moreover, despite its frequent use, it is not generally accepted as proof of identity as the same cell can look different depending on how it was cultured. Nevertheless, photomicroscopy is still useful for training, cell culture maintenance and record-keeping.

Genotyping is another required test defined by ICH Q5D. For this type of testing, full DNA sequencing is the most foolproof method, but it is expensive and time-consuming, and so is not always practical. Faster surrogate techniques can be considered; banding cytogenetics or DNA analysis (either using gels or qPCR) can detect a genomic polymorphism pattern. Such "fingerprinting" can provide confirmation of species of origin and known unique cell line markers – and is definitely considered an adequate test of identity. To be clear, such level of detail is not explicitly required for an analytical cell bank. However, if available, it is a characterization test that can provide important supporting data for the use of that cell line.

For an analytical cell bank, although it is good practice to confirm the cells' identity, it is far more important to know whether the cells will respond to the therapeutic being tested in a predictable fashion. Information about cell line stability is essential, including the number of times the cells can be doubled before the functional response begins to shift significantly. It is possible for a non-pure population of cells, or an unstable genotype, to outgrow the desired cells, which will result in loss of functionality of the cell bank.

Similarly, for phenotypic identity, a combination of methods should be considered, including microscopy. Protein secretion analysis, either via ELISA or protein arrays, is more exacting, and flow cytometry or electrochemical luminescence (ECL) can be used to study cell surface protein expression. At the molecular level, reverse transcription-qPCR or microarrays can be effective for examining mRNA expression. You should also consider biologic functionality when looking at phenotype, and how this changes in response to the therapeutic – death, apoptosis, proliferation, or a change in the proteins that are secreted or expressed on the cell surface. Also, consider how this changes over multiple population doublings.

It is also important to consider how the cells will be used in the assay. For cells that are maintained in a continuous culture, the cells must remain in optimal condition on every culture passage. Cells should not be subcultured based on a volumetric ratio; rather, this should be done based on numbers of cells per milliliter or square centimeter. The cells must be in log-phase growth at all times, and every stress condition, such as over- or under-growth or nutrient deprivation, has the potential to cause a change in their behavior. In fact, continuous culture is a common source of variation in bioassays.

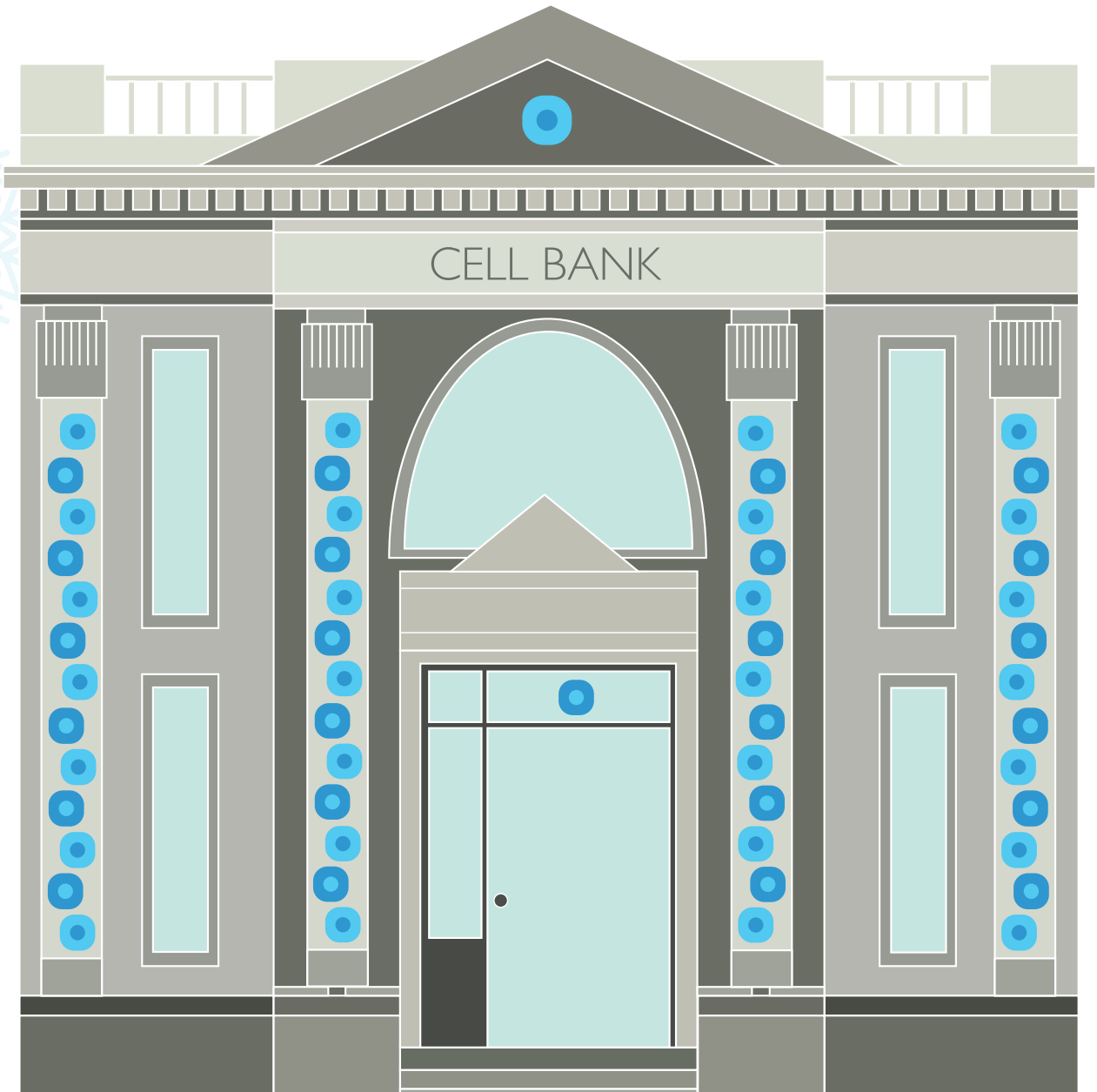
An alternative strategy is to use a technique such as "thaw and go". Cells are frozen from culture, with a per-vial density sufficient for more than the 96 wells on a microtiter plate. The cells are used immediately, or within 24 hours, being placed directly into the assay once they have thawed. The cells should be as healthy as possible before they are frozen, although it may be necessary to filter out cell culture aggregates. This strategy significantly reduces the potential for stressed culture condition, because the cells simply become a critical reagent once they have been qualified.

Banking on bioassays

R&D banks save time by allowing assay optimization, and even some prevalidation, while the GMP bank(s) is/are being generated and validated – a real benefit. And if the banks are protocol-documented, they can provide supporting scientific data for future GMP production activities.

To create a bank, you can use multiple 175 cm^2 culture flasks for both adherent and non-adherent cell lines. Cells can be harvested using 50 mL polypropylene centrifuge tubes, and then pooled into a single centrifuge tube, washed several times, before being quantified using trypan blue viability tests. The next step is to re-suspend the cell pellet in an appropriate volume of chilled cryopreservation medium, which is then split into 1 mL aliquots in separate cryovials. These are then frozen using liquid nitrogen in a controlled rate freezer. Such a manual technique is practical for up to about 100-150 vials, but you need to take care when it comes to maintaining homogeneity of the vials, as the cells will settle while they are being aliquoted.

It takes around 21 weeks to prepare a cell bank: five weeks for preliminary testing, three weeks to produce and a further five weeks to characterize the master cell bank. A similar eight-week timespan accounts for the production and characterization of the working cell banks, and then the vials should



Watch Out For...

- Generating smaller sized GMP analytical cell banks (especially working analytical cell banks, or WACBs) may be tempting if resources are limited. The trade-off is the high likelihood that "absolute" assay responses may shift significantly between banks as a result of a combination of different culture passage numbers and potentially different culture conditions. While generated relative potency values, by definition, ought not to be impacted, curve dynamics, and thus data analyses, may well be impacted.

  Response: It is well worth doing whatever is required to resource for making as large a bank as may be needed for at least a 3 to 5 year period. This is especially true for thaw and go WACB.

- Aliquoted cells may not survive the freezing process. This may manifest in several ways. The most drastic is that the cells are completely nonviable upon thawing. More subtle, but no less impactful, effects may be that the cells are overly stressed (with lowered viability) upon thawing, but can recover in culture. While apparently fine, these cells may no longer respond to ligand in the way that they did prior to freeze. If the cells are intended for thaw and go use, then there would not even be the possibility of in-culture recovery.

  Response: To begin with, it is important to test and identify the best freezing media for your particular cell type. Secondly, if at all possible, use a controlled-rate (step) freezer, either LN2-based or mechanical-based. While the "Mr. Frosty" type -80C freezer containers do work reasonably well and are able to achieve a slowed rate of freezing, they are not actually controlled. A controlled-rate freezer is designed to customize and differentiate the rate of temperature drop for prior, during and after the freeze transition phase. Viability is significantly more assured using the controlled-rate systems.

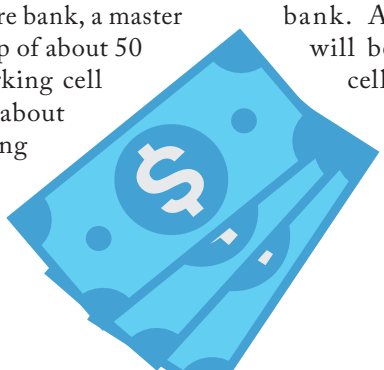
- Cells may be stable for either growth or response characteristics for only a limited number of generations/passages. This may be due in part, for continuous culture cells, to a non-pure cell line, so that a non-responding subpopulation outgrows the responding population. For engineered responder cells, it could be due to a DNA construct that is either directly unstable or is somewhat deleterious to cell health and is selected against during normal in-culture genetic drift. For primary-cell-based assays (e.g., HUVEC) the cell may inherently only be capable of a very limited number of divisions before they senesce, unable to maintain their necessary phenotype.

  Response: This is one of the many benefits of developing and utilizing a thaw and go WACB strategy. Following a very limited number of cell divisions, the bank is then set. This means that the cells may then be used for the lifetime of that bank with no more (or one to two more,, depending on cell/assay requirements) cell divisions.

go into secure long-term storage, which of course should meet GMP conditions.

Your cryopreserved banks should, ideally, be stored in two geographically separate locations or, if this is not possible, in two separate locations within the same facility. If the cells must be shipped, they should be split into at least two shipments, with temperature monitors to ensure they do not thaw. If something happens to one shipment, then at least the entire bank is not lost!

The number of frozen cells required depends on the type of cell bank. If it is a continuous culture bank, a master bank will be made up of about 50 vials, while the working cell bank will contain about 100 vials. Assuming one vial is thawed every two months, each working cell bank will contain enough cells for about 16 years of bioassays. The numbers are slightly different for a thaw and go culture bank. Again, about 50 vials will be made for the master cell bank, but at least 400 vials will be generated for the working cell bank. At a usage rate of four plates per week,



"Bioassays are a fact of life for the testing and release of biologics."

this will provide sufficient cells for about two years.

The big challenge here is securing sufficient biomass to fill 400 vials! Using cell cubes, stacks or towers rather than standard flasks is more space efficient, but there are some newer technologies that can make the process easier; I recommend wavebag-type technologies (e.g, the Xuri W25; GE Healthcare), which are designed for non-adherent cells, but can support adherent cells using such strategies as microbeads.

Bioassays are a fact of life for the testing and release of biologics. Analytical cells, in turn, are a fact of life for bioassays. Thus, relative potency data for CMC testing and release, and the bioassays from which these results are derived, depend on the availability of dependable analytical cells. Stable and predictable cells are essential for running accurate and reproducible bioassays – and a well-planned, executed and validated analytical cell bank can save you a lot of time, while meeting regulatory requirements for bioassays.

Mike Merges is Director of Strategic Growth of Biologics Analytical Services, and Mike Sadick is Principal Scientist, Biologics Analytical Services, both at Catalent.

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Taking Charge – Come Rain or Shine

Are people born to lead or can they be cultivated? Here, I share how we take a proactive approach to discovering and investing in future leaders.

By Louis Fioccola

Leadership qualities are highly prized in today's competitive pharmaceutical market. After all, the right leader can guide a company from a second-tier position (or below) into the upper echelons of its sphere of business by motivating and inspiring colleagues and employees. But all too often "leadership" as a concept can be confused or conflated with a specific role, title or position within the hierarchy of an organization. In reality, leaders can emerge at all levels within a business – from the boardroom to the shop floor – regardless of job title and function. At my company, Cambrex, everyone is expected to lead wherever they are in the organization – and I believe this is a good direction for a company to take.

Decision makers who are based in the "ivory tower" of a company's headquarters are often far removed from the actual processes and products. To be successful, you need those who are closest to the products and to the customers to feel empowered to make decisions that will improve the business. The traditional role of a leader is to set the pathway for moving forward and to bring everyone along with them, and it is still crucial to show leadership by example. To use an old cliché, a leader must "walk the walk, as well as talk the talk." I believe that a leader must be able to inspire people with their experience, by their presence and other traditional qualities – but they must also be willing to get into the trenches with them. You need someone who says, "Look, this is going to be difficult, but we have to get in there and do this. We are up against some crazy odds, but here is how we can get there and I am going to roll up my sleeves and do this with you."

"You need to have leaders who are setting an example through clear communication and clear expectations."

Cambrex has always been relatively lean with few layers of management, and most of our senior team have come up through the operational side of the business and have the ability to interact genuinely with all levels of the organization. Our Chief Operating Officer, Shawn Cavanagh, is a chemical engineer who has worked his way up through the company into a leadership role. It is so important to be able to inspire someone on the shop floor, as well as someone on the executive team.

Leaders must be able to connect with someone in the plant talking about processes as readily as discussing M&A strategy around the boardroom table, and must be able to paint a picture and get people to share a vision.

Another essential quality in a leader is discipline that translates into process and order and setting a rhythm for the organization. Typically, the culture of an organization is set from the top, and you need to have leaders who are setting an example through clear communication and clear expectations.

The true test of a good leader is not how they behave when things are going well, but how they show what they are made of when things aren't going so well. It is fairly straightforward to manage a process or a project when everything is running smoothly and all the resources are in place; how could you not be successful in those circumstances? But if there is a major issue with a customer, which is potentially costly in terms of money and reputation, does that leader bluster and rage? Do they blame others? Or do they bring everyone together, gather the best ideas, find a solution and galvanize the team into moving forward? That is the kind of leadership that is the most valuable – leading by example, but still remaining open to suggestions.

It is in response to the worst-case scenario where true leaders distinguish themselves from tactical managers. Organizations will always have their ups and downs, resulting from changes in the market or the regulatory landscape. There are always high points and valleys; the questions is: how do you get out of the valley and up to the next high point? Things will inevitably go awry at times, and if a leader cannot control their emotions when challenges arise, and fails to understand that their role is to create a sense of calm, then the company has a problem. In my 20-year career, I have seen people who are extremely well-educated with fantastic pedigrees who struggle when things don't go their way – sometimes to the point where you wonder if you are working with a 50 year-old executive or a five year-old child! Prior to joining Cambrex, I witnessed leaders at other

My Top Leadership Tips

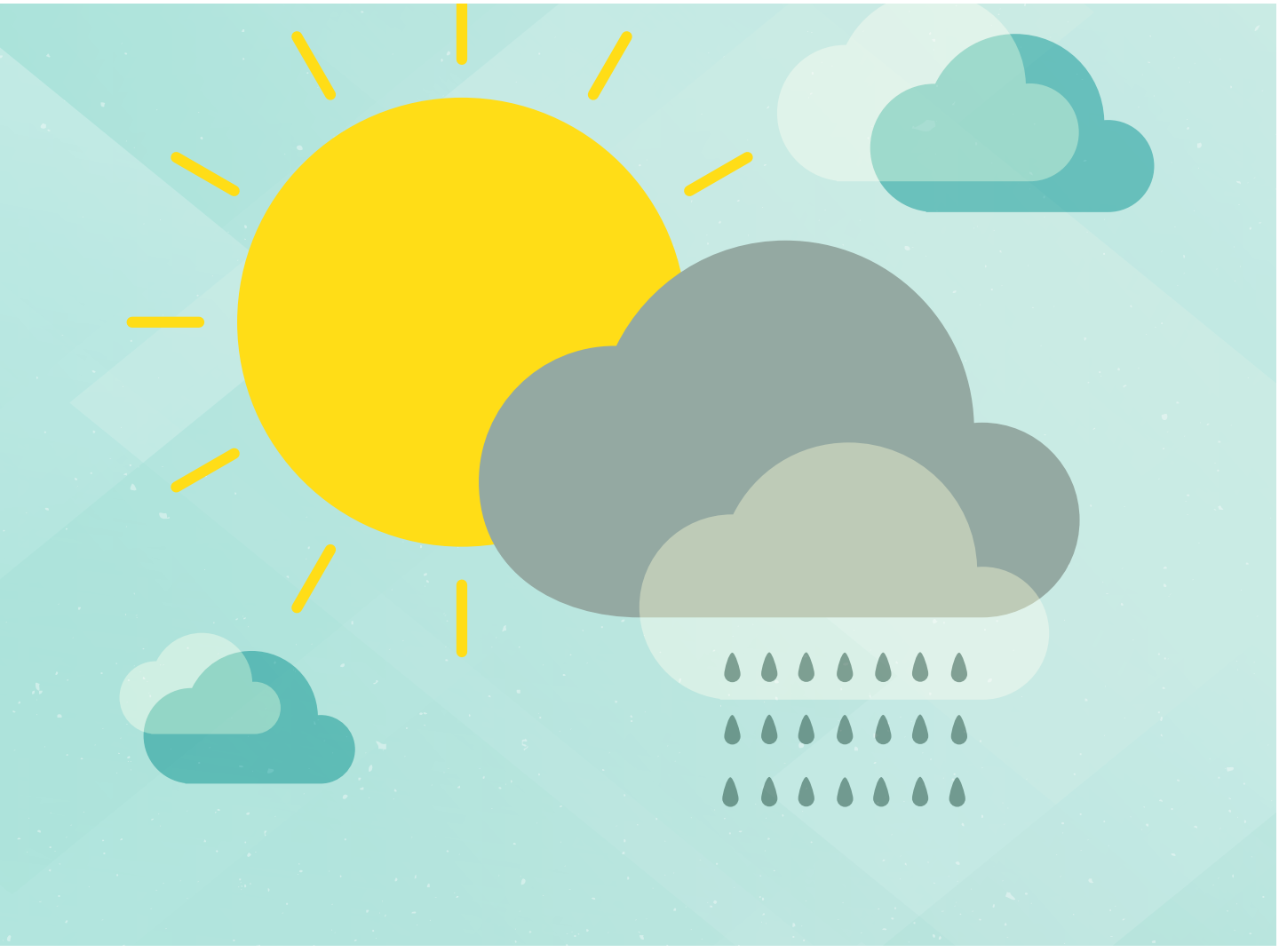
Communicate expectations clearly and test for understanding.

Expect things will go awry; that is when your ability to lead will be tested.

Take accountability; own the outcomes of your actions and those of your team.

Foster a culture where everyone understands that they are expected to lead from their role in the organization.

Tap into the knowledge of those who are closest to the product and the customer.



companies who were lauded for their leadership while the organization was doing well. But as soon as the landscape changed, they became "absentee leaders" because they did not want to be tainted by the lack of success. They enjoyed the celebrations and basked in the glory of the successes, but when things were not going so well, they were quick to blame others.

Cultivating talent and leadership

A large part of being a good leader comes down to temperament: how a person handles the challenges, and interacts with others during tough times. Humans will always make errors, but there is a difference between a person who berates a subordinate for it, and a true leader who looks for a way to fix it constructively.

If leadership is a matter of temperament, it begs the question whether people are born to be leaders, or whether they can be taught. I think that to a large extent it is a personality trait, but I also believe leadership skills can be learned over time and through

"It begs the question whether people are born to be leaders, or whether they can be taught."

experience. Over the course of peoples' careers, most have seen examples of good and bad leadership, which may lead them to aspire to be like the former, or vow to never behave like the latter.

My role over the past five years has included building a very robust talent calibration process that measures an employee's performance in their role, but that only tells part of the story. In particular, we are looking at how an individual responds to being exposed to different stresses and how they handle themselves in given situations. For example, one individual may be very adept at handling change: they can see change coming, appreciate the need for it, and handle it effectively. On the other hand, another individual with a similar background in the same role may not be able to cope with change because they rely heavily on a routine. When we add into the matrix real work examples and feedback from managers, colleagues and subordinates, we can identify those with high potential for leadership.

From there, we look to see how we can best invest in them, and what development they need to complement their skills to take them to the next level. These individuals are the future of the business. Every company will have key leadership roles and you want to ensure you have the best people to fill them! In my eyes, it is crucial to look at what you need talented employees to do to enable them to continue to grow and be successful.

In our industry, like many others, we need to be nimble and flexible. Cambrex is a contract manufacturing organization and our clients range from big pharma to small and emerging companies, so we have to be prepared to look at what is new and coming along, and how we can add value to it. We are constantly looking for people with agility in a range of different situations – with regard to change, performance, learning and interacting with people. We need to attract, retain, develop and motivate talent, and these four basic principles are applied to recruitment, through development, learning and training to succession planning.

True leaders are those who show up at the toughest times and also have the will to make dispassionate decisions on how to move forward, while encouraging colleagues to put their best ideas forward too. Investing in people who have that potential means you are investing in the future success of the company.

Louis Fioccola is Senior Director, Global HR Cambrex, East Rutherford, New Jersey, USA.

Digital Driver

Sitting Down With…Kal Patel, MD, Senior Vice President of Digital Health for Flex.

Were you always interested in technology?
I'm not a tech native. I'm a physician and MBA by education and I've never been the first person to run out and buy the latest and greatest technologies, so it has perhaps been surprising how my career has panned out! I spent some time working for the Boston Consulting Group across various parts of healthcare, and then I moved into pharma; first at Novartis in various sales and marketing roles, and then at Amgen. I did a lot of work with Enbrel at Amgen and I began to see the gaps between what patients needed and what pharma - and the healthcare systems in general - were delivering. For example, by six months, at least a quarter of patients prescribed a drug become non-adherent, despite having a chronic disease. The best drug in the world won't work if patients won't take it!

How did you come to focus on digital health?
As part of a broader transformation within the company that the CEO of Amgen was driving, he asked me to look at how technology was changing and what implications it could have for the pharma industry. At the outset, I wasn't really sure he'd picked the best person for the job given how many basic questions I had about different technologies, but I did a deep dive into the space and it was incredibly eye opening to see the possibilities.

At Amgen Digital Health, my group's focus was on improving the real-world performance of drugs by looking at three areas. The first was adherence; how do we capture data about what is happening on the individual patient level and use that information to drive better engagement and adherence? Second was building algorithms that could help identify patients that were either under treated, misdiagnosed, or inappropriately treated where Amgen had a viable therapy; we wanted to find these patients and get them onto a better treatment plan, which involved working closely with different electronic medical record solutions and patient registries in key disease areas.

The third category was broadly described as digital marketing. We had programs that significantly improved our understanding of what information patients were actively seeking and delivering that content more effectively; we also improved the personalization on the prescriber side as well.

What came after Amgen?
I went to Silicon Valley and I was recruited to serve as chief commercial officer of Doctor On Demand, now the largest US video medicine provider, which brought me even closer to patients. I think that being able to access a doctor is a real pain point and my role was to drive the business and platform from just being a direct-to-consumer product to one that patients could access through traditional employer-sponsored health plans.

Today, I lead Flex's digital health business and I think I have the best of both worlds. Within a traditional pharma company, you're trying to drive transformation from the inside, while at a tech startup, you're trying to drive digital disruption, in some ways outside of the healthcare system. Flex Digital Health is very entrepreneurial and yet has the massive global scale of the broader Flex organization to help facilitate digital disruption. Our focus is on connecting medical devices and combination products and aggregating and analyzing real-world data to enable our pharma and medtech customers to optimize their therapies and devices.

What digital technologies are you interested in?
Generally, technologies hit the consumer market before the regulated market, and looking at the trends on the consumer side I am very excited about the future of wearables. It is a great way to make people more aware of their health – and medical-grade wearables can easily generate valuable patient data. But pharma should also be looking at how to bring connectivity into drug delivery. The penetration of digital technologies, particularly smartphones and voice-based devices, into patient's everyday lives today presents a huge opportunity for pharma companies.

Another technology to watch is AI and machine learning – despite all the hype, this area is advancing rapidly. No physician or person can keep up with the explosion in relevant knowledge no matter how much they study. Machines can help doctors accelerate and improve diagnosis, determine which cases require more time/deeper analysis, which patients are likely to adhere to which type of therapy, and so on.

Why aren't pharma companies focusing on digital solutions?
Very few CEOs or boards are asking the right questions. Pharma companies still take a traditional approach to innovation spend. Instead of asking what new drug development programs they should invest in, they should ask, "Where should we invest our money for the most clinical and financial ROI?" If they ask that question, it's hard to imagine how you don't reallocate billions of dollars into technology to dramatically improve adherence, patient identification, high risk adverse event monitoring and predicting, and so on. There is no doubt that we need more effective treatments in almost every therapeutic area, but is pharma going to generate the most value by pouring nearly 100 percent of innovation budgets into developing new drugs? A few billion poured into R&D might lead to a new drug or it might not, given that success rates are low. But the same amount of money poured into digital would almost certainly produce disruptive innovative solutions that could improve clinical outcomes, the patient experience and drug makers' stock prices.

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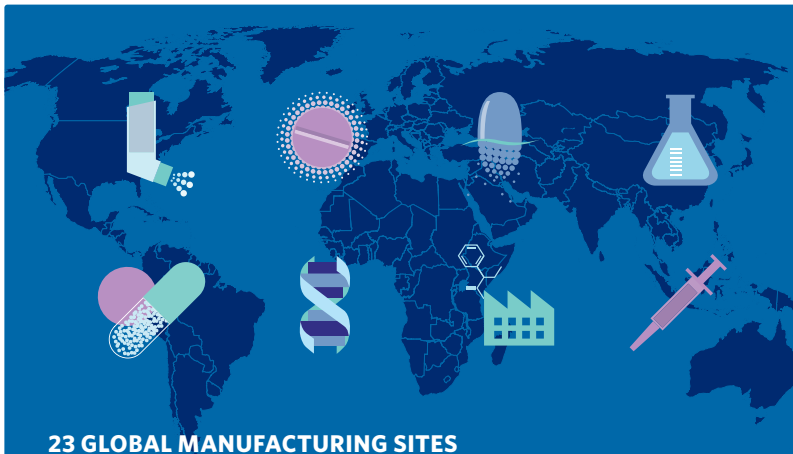

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