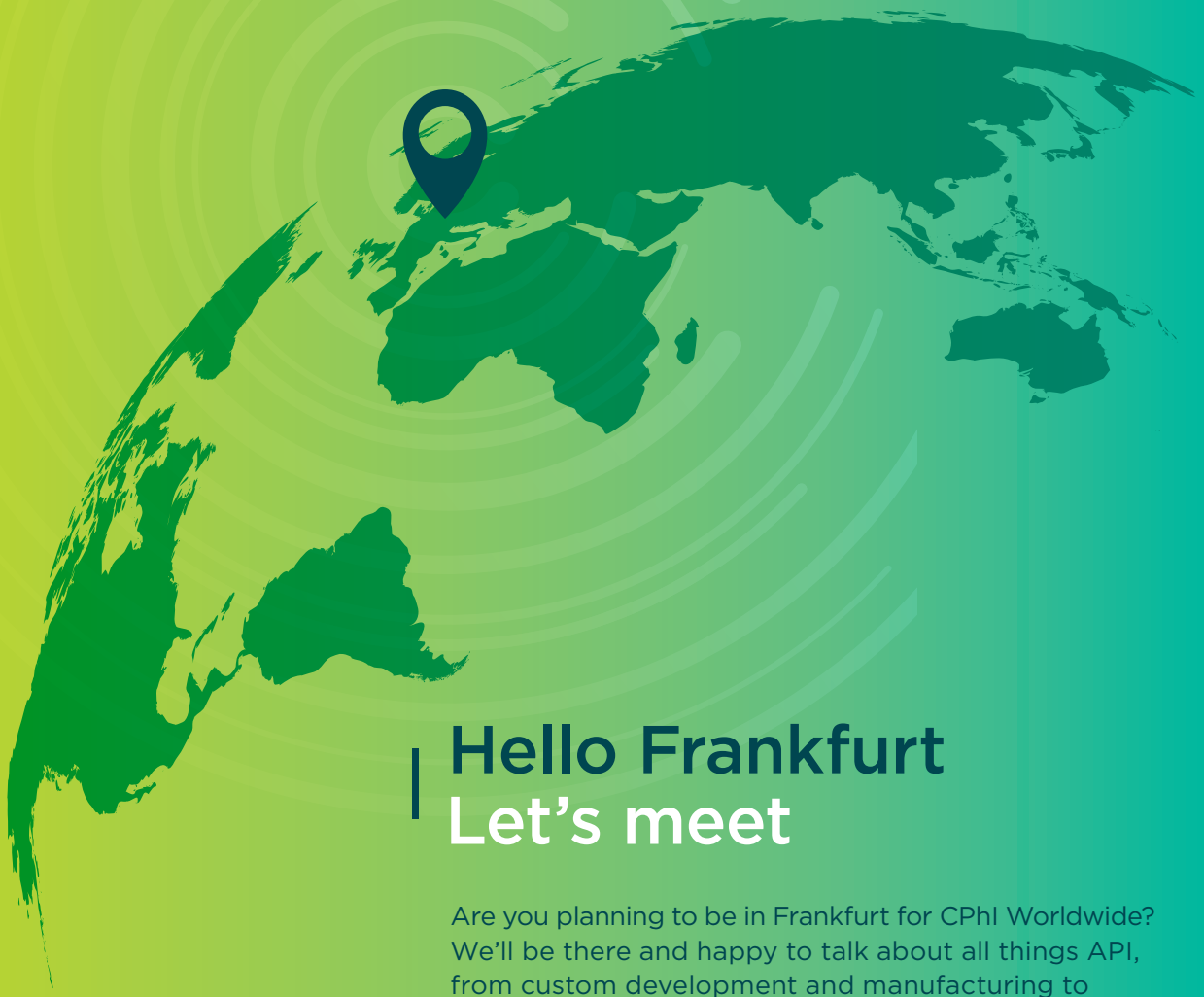
OCTOBER 2017 # 34

the Medicine Maker™

Weathering the Globalization Storm

Can pharma regulators find perfect harmony amid the sea of change?

CPhI Worldwide
Frankfurt
24–26 October 2017



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Online this Month

Tackling Globalization

What does globalization mean for regulators? This month's feature on page 20 examines pharma's global regulatory landscape and the march towards global cooperation, convergence and harmonization of standards. You'll find more related content on our website, including pharmaceutical market systems in the developing world, and differences between EMA and FDA approval times.

Read more at http://tmm.txp.to/0917/Harmonization

Taking on CPhI

The Medicine Maker team will be attending CPhI in Frankfurt, October 24-26. Keep up to date with our thoughts on the show via our Twitter feed @ medicine_maker, or drop by our booth (KH01 and KH02) to say hello.

All in One

Can microparticles enable multiple vaccines to be delivered in a single injection? A recent project by the Langer Lab at MIT would suggest so. The group has developed microparticles described as resembling "cups." A vaccine or drug is placed in the cup and sealed, and then released at a specific time. Different vaccines can be placed in different cups that release at different times.

Read more about this fascinating research at http://tmm.txp.to/0917/Langer

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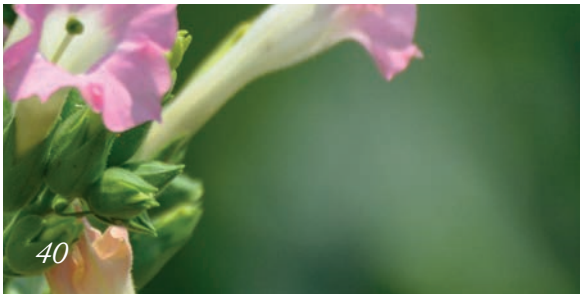

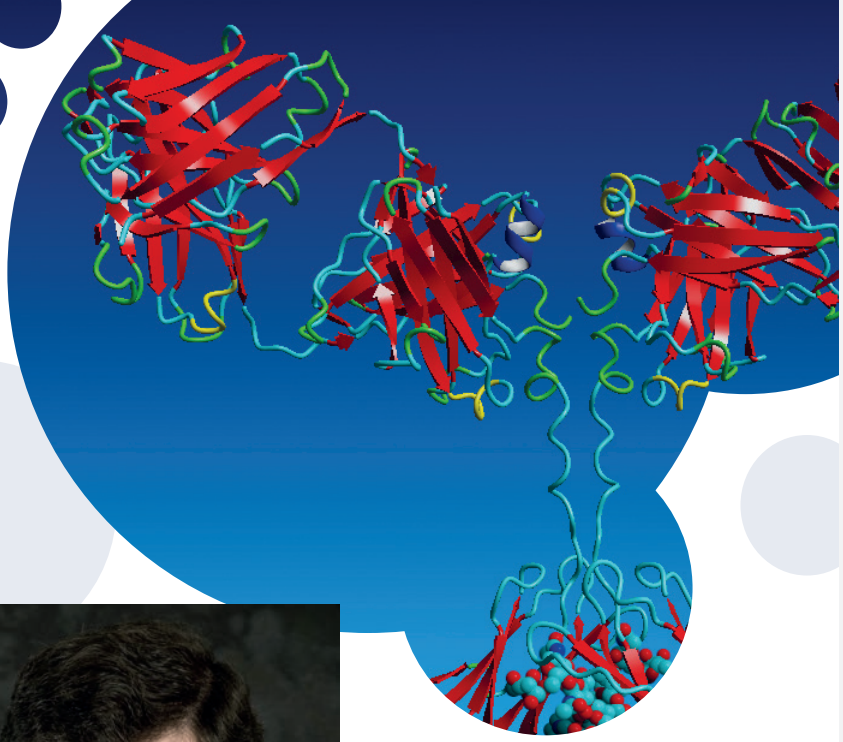

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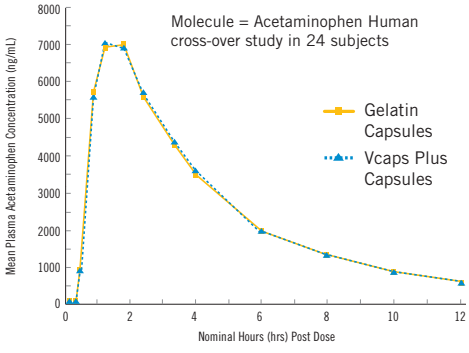

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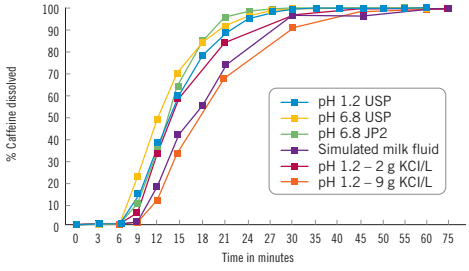

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Safe Supply Chains for All

Despite the fantastic technologies at the industry's disposal and increasing efforts to round up counterfeit criminals, fake medicines still find their way into supply chains.

Last month, we covered the hot topic of serialization (catch up at tmm.txp.to/0817/Serialization, if you missed it). Since then, I've been fortunate enough to speak with Ken Brown, the Executive Vice Chancellor of the University of Tennessee. Brown has also been involved in the Asia Pacific Economic Cooperation (APEC) effort to develop the Supply Chain Security Toolkit (1). The University of Tennessee's Health Science Center is designated by APEC as a Center of Excellence in global medical product quality and pharmaceutical supply chain security, and Brown's personal passion for the supply chain was moving. Indeed, he described it as one of the single most important topics in the industry. Firstly, counterfeit and falsified medicines cause serious harm or death – either directly or indirectly. Secondly, this serious crime undermines all of the effort that goes into building and training a reputable pharma and healthcare industry. Look forward to reading the full interview with Brown in a future issue.

Unscrupulous individuals and counterfeiting will always exist where profit can be made, so it's a constant battleground. Interpol's "Operation Pangea" took place at the end of September, resulting in the seizure of illicit or counterfeit medicines worth more than $51 million, and 400 arrests worldwide (2). The operation takes places annually at a different time each year, and involves Interpol, police, customs, and health regulatory agencies. Thanks to such efforts, plus new technology, regulations, and the work by APEC and others, it is becoming increasingly difficult to slip illicit medicines in legitimate supply chains in Europe and the US (discounting the proliferation of dubious sources on the Internet).

But what about low- and middle-income countries, where counterfeiting is an even bigger killer? Cheap, portable analytics are one potential solution to combat the problem – and the positive impact of one such system was highlighted recently by the 2017 Humanity in Science Award (3). Richard Jähnke from the Global Pharma Health Fund received the award from our sister publication, The Analytical Scientist and its partner, KNAUER, for his work on the GPHF Minilab – a field kit for medicine quality analysis. More than 800 Minilabs have been put into service, detecting falsified medicines in 95 countries.

With so many determined individuals working so hard to combat the problem, can we one day hope for a time when the chance of a patient receiving a dangerous counterfeit product is very much reduced worldwide? After all, access to safe medicines should not be limited by geography.

Stephanie Sutton
Editor

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2. *Interpol, "Millions of medicines seized in largest INTERPOL operation against illicit online pharmacies" (2017). Available at http://bit.ly/2g1iWgp. Last accessed October 11, 2017.*
3. *The Humanity in Science Award, www.humanityinscienceaward.com*

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

IP Deal or No Deal?

The future status of pharma intellectual property in the UK depends on the outcome of Brexit

With British politicians scrambling to define Brexit, UK pharma companies are currently in the dark about what breaking away from the EU will mean for business. According to experts from patent attorney Beck Greener, one of the (many) difficult questions about Brexit is, what happens to pharma's intellectual property? Currently, British-based pharma IPs are covered under the European Commission's Summary of Product Characteristics (SPC), but if an appropriate deal isn't struck between the UK and EU, it could lead to an IP grey-area.

"SPC protection will almost certainly be available to UK-based pharma companies post-Brexit, but what they'll have to do in order to obtain that protection largely depends on the outcome of negotiations," says Jamie Fraser, UK and European patent attorney at Beck Greener. "However, if the Brexit negotiations end in a 'no-deal' situation, there may be no other option for UK-based pharma companies than to expand or relocate at least some of their business to an EU member state."

Fraser recently co-authored a paper outlining the potential consequences of pharma IP and SPCs (1), which raises the possibilities of both "hard Brexit" and "soft Brexit" scenarios. Regarding market authorization (MA) in relation to the EU, the paper stated, "A recent EU Commission and EMA Notice (EMA 2017a) would appear to be a warning shot to UK-based companies who currently hold an MA issued by the EMA. The notice reiterates certain residency and activity requirements for MA holders (EMA 2017b):

- EU law requires that marketing authorization holders are established in the EU or EES.
- Some activities must be performed in the EU or EEA, related for example to pharmacovigilance, batch release, etc." (1)

The European Commission has also released a paper discussing potential post-Brexit IP rights (2), in which it is stated that a person or company should continue to be allowed to keep their IP application, but Fraser adds that it is still unclear about what lies ahead for future applications. A factor that could affect the future is the UK repeal bill (depicting what EU laws will be adopted to the UK for ease of transition), and the subsequent amendments that will be made to it. Fraser says, "If the UK intends to directly transcribe existing EU law into the new UK statute, this would mean that the UK would continue to recognize the legal validity of MAs issued by the EMA. Therefore, an SPC granted in the UK that is based on an MA issued by the EMA would continue to be considered valid and in force in the UK."

Fraser and his co-author explain that the UK could agree to remain bound by EU law for IP matters, although this is difficult to imagine in the current political climate. Instead, Fraser recommends that companies look into the issue so that they are ready to make a move when the situation becomes clearer. *WA*

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1. *J Fraser, J Stones, "Brexit – What are the potential consequences for pharma patents and SPCs?", B J Pharm, 2, (2017).*
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Navigating the Nose

Could a new nasal delivery method finally get drugs to the central nervous system?

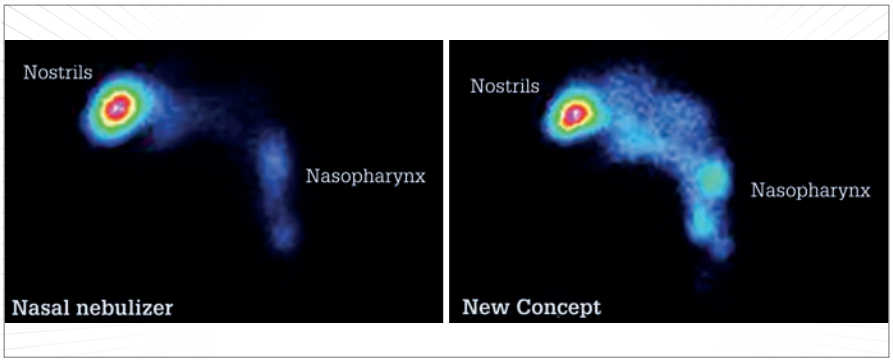


Figure 1: Scintigraphy images of deposited aerosol in the human nasal cavities (lateral view) for nebulized aerosol (5µm particle size) by the nose (left image) and the same nebulizer used with the new concept (right image).

Nasal drug delivery is considered non-invasive and can provide rapid therapeutic results – but it is also challenging because the nose is designed to filter out hazards rather than absorb drugs. Getting drugs to the upper nasal passages and the olfactory region is particularly difficult, but could open up the possibility of targeting the central nervous system.

A partnership between the University of Tours, France, and drug device specialist Nemera, aims to offer a boost to nasal drug delivery. Researchers at the university have developed a new delivery method that they believe will allow for better drug deposition in the distal region of the nasal cavities, and make the most of the influence of nose anatomy to decrease deposition variability.

"The University has patented its new method of delivering drugs to the nasal cavity and was looking for a partner to co-develop a disposable delivery device. The University will be focusing on experimental testing, mainly consisting of in-vitro deposition studies, and we will be working on the device and testing materials," says Alain Regard, Technology Product Manager at Nemera.

Initial proof of concept has been performed for the delivery method using jet nebulizer technology. The University of Tours and the Aerodrug department of the Diffusion Technique Française measured the influence of small particle sizes (from 2µm to 10µm in terms of mass median aerodynamic diameter) on the deposition distribution in a nasal cast model using their new method. Laurent Vecellio, Scientific Director of Aerodrug, and a member of the research team at the University of Tours explains in more detail: "Our method involves delivery of the drug through the buccal cavity during the nasal expiratory phase using a small portable device. The drug particles enter the nasal cavities through the rhino pharynx, which has a significant impact on drug deposition," (see Figure 1).

You can read more about the challenges and potential of nasal drug delivery on page 16. *SS*

Destination Innovation

Nominations close on November 10 for The Medicine Maker 2017 Innovation Awards

Pharma manufacturers face many challenges in today's world when it comes to making medicines that are efficient, affordable, and have an edge over competitors. The right equipment and services can make a huge difference, and vendors are constantly innovating to raise the bar. Every year in December, The Medicine Maker celebrates the most groundbreaking new technology to hit the market via the Innovation Awards. And it's up to you, our readers, to choose which products deserve to be showcased.

Entries for the 2017 Innovation Awards are open, but will close on 10 November, so you'll need to act fast. To be eligible, a product must have been launched (or will be launched) between January 2017 and December 2017. The "product" can be equipment, software, technology or even a service relating to any area of drug development, manufacture and formulation. We accept entries from vendors, but also welcome submissions from users who wish to highlight an exciting technology that has revolutionized their laboratory or facility.

To enter, fill out the quick form at http://tmm.txp.to/innovation-form2017, or drop an email to stephanie.sutton@texerepublishing.com, with the subject line "Innovation Awards".

Previous winners include an open innovation platform from LEO Pharma (2015) and MilliporeSigma's (known as Merck KGaA in Europe) Centinel Intelligence Virus Defense.

We look forward to honoring our 2017 winners in the December issue of The Medicine Maker. *SS*

Saving Lives by Design

An exhibition in London explores the relationship between graphic design and health

Street artist Stephen Doe paints an educational mural about Ebola in Liberia, 2014. Credit: Dominique Faget/AFP/Getty Images.

What? "Can Graphic Design Save Your Life?" is an exhibition showcasing the role of graphic design in communicating healthcare messages. More than 200 objects are featured in the exhibit including packaging, health-related posters, comic books, hospital design, pharmacy signs, and more. The exhibition also includes items from the archive of Burroughs Wellcome & Co., one of the first companies to market directly to doctors and to rigorously enforce trademarks and brand, which provide some of the earliest examples of corporate identity in the pharma industry. In addition, the exhibition considers how graphic designers deliver clear healthcare instructions to consumers through carefully designed color coding systems, written instructions and pill packaging.

Why? According to Ken Garland's "First Things First" manifesto, graphic designers should use their skills for good. Graphic design has the power to shape public perception around healthcare and epidemics, and empower people to respond.

Who? The exhibition has been curated by graphic designer Lucienne Roberts and design educator Rebecca Wright, founders of publishing house GraphicDesign&, with Shamita Sharmacharja at Wellcome Collection.

Where? Wellcome Collection, Euston Road, London, UK.

When? The exhibition will run until January 14, 2018.

Skin in the Game

Could donated skin be a viable alternative to animal testing?

Genoskin – a French National Center for Scientific Research (CNRS) spinoff – believes there is a better alternative to animal testing when it comes to dermatological and cosmetic research: donated human skin, which it collects from surgical procedures. Keeping the skin "alive" using an ex vivo culture system, the company is able to provide skin samples in the form of slide sections, frozen tissue, or epidermal to hypodermal sections.

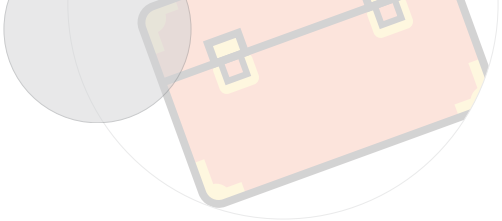
"I have previously worked with transgenic and knockout mice to investigate the function of a particular gene in skin development," explains Pascal Descargues, CEO of Genoskin. "The mouse models were very useful in discovering new molecular pathways, but we were not able to confirm the results for humans because we were missing key comparable elements. Furthermore, we found that a mouse model reproducing the skin disorder Netherton Syndrome could not be used to screen drugs at all since the disease is lethal for mice."

Descargues initially started the Genoskin project during postdoctoral training at the Paul Sabatier University/

CRNS to offer more in vitro tools for skin researchers, but ethics were also a consideration. "I was never comfortable with the ideal of performing experiments on mice and killing them," he adds.

Some researchers have turned to lab-grown skin to address the same problems, but Descargues argues that synthetic skin does not offer the same benefits as the real thing. "Reconstructed or bio-printed skin models face many limitations, including immature barrier function, absence of immune cells, no dermal extracellular matrix, no adipose tissues, and the absence of skin appendages like hair follicles. All of which mean that synthesized skin may not be as accurate a predictive model for testing parameters, such as dermal absorption, allergies, or for testing sub-cutaneous injections."

Collecting skin samples requires ethical committee approval, agreements with hospitals, and donor consent, but a small amount of skin can go a long way. In 2016, Genoskin collected 100 skin samples, which they turned into 1000 skin models. "There are more than 20,000 abdominoplasties carried out every year in France alone – and more than 200,000 in the US – and skin could make a real difference to testing. I am convinced that, at least in dermatological and cosmetic research, we could one day replace all animal testing worldwide." *WA*



Business-in-Brief

Record generic approvals, a joint opioid investigation, and emerging technology guidance... What's new for pharma in business?

Approvals

- This year marks another record for the number of US generic drugs that have been approved. The FDA has approved 763 generics (927 if tentative approvals are included) during their 2017 fiscal year, which ended October 1 – 112 more approvals than 2016, continuing the upward trend of generics approvals over the past few years.
- A study published in the BMJ set out to determine the quality of life benefits that chemotherapeutics in Europe offer (1). The researchers studied drugs approved by the EMA between 2009–2013, and to the surprise of many concluded that most of those drugs showed little to no benefit for quality of life or survival. The study included data from a minimum of 3.3 years after market entry, and found that the chemotherapeutics offered marginal survival gains over existing treatments or placebos.

Controversy

- Following Allergan's controversial patent deal with the Saint Regis Mohawk Tribe, four US senators have co-signed a letter to the Senate Judiciary Committee Chairman to combat the action. They describe Allergan's deal with the Tribe for their eye drug Restasis as a "blatantly anti-competitive attempt to shield its patents from review and keep drug prices high". Their letter calls for an investigation into the unique scenario, as the senators believe that companies should not be allowed to pay Tribes or States to invoke their sovereign immunity at the expense of patients.
- A coalition of 41 attorneys general in the US have banded together to investigate opioid marketing practices and have issued subpoenas to several pharma companies including Endo, Janssen, Teva, and Allergan. A supplemental investigative subpoena has also been sent to Purdue Pharma, and some distributors have also been asked to hand over documents. In a letter to America's Health Insurance Plans, attorneys general also urged insurers to prioritize non-opioid treatments.

Regulation

- The EMA has issued an update about its relocation plans post-Brexit. The agency has received bids from 19 EU countries and has performed a thorough assessment of each. Currently, the preferred options appear to be Amsterdam, Barcelona, Copenhagen, Vienna, or Milan. The assessment considered the proposed buildings, accessibility of location, existence of adequate education facilities, appropriate access to the labor market, social security, medical care, and business continuity. Potential staff retention for each candidate location has also been considered. EU member states will vote on the move in November.
- The FDA has released a guidance to help advance novel technology that could potentially improve pharma manufacturing, such as continuous manufacturing and 3D printing. The document "Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization" offers recommendations to companies that wish to participate in the FDA's Emerging Technology Program, which provides a route for companies to engage with the FDA early on, prior to regulatory submission, when considering new emerging technologies. The scope of the program focuses on new technologies that have the potential to "improve drug product safety, identity, strength, quality, and purity". *WA*

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For links to the source material, visit the online version of the article at: http://tmm.txp.to/0917/business

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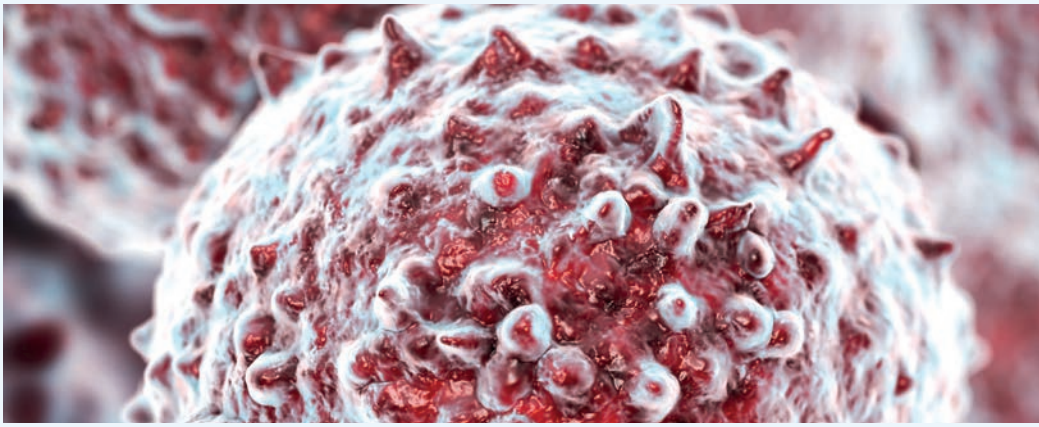
Automating the Future



The era of cell therapies is upon the industry. To ensure that processes run smoothly, safely, and cost effectively, we must embrace a more automated approach.

Biopharmaceuticals are typically more difficult to manufacture than small molecule drugs, but cell and gene therapy products pose even greater challenges. When working with stem cells, agitating the cells even slightly too much when they are growing on microcarriers, for example, could stimulate the cells to differentiate along the wrong pathway, affecting yields and potentially creating the wrong product. Other steps in the manufacturing process, such as cryopreservation, can also affect cell viability, so it is crucial that cell therapy producers understand both their product and every step of their processes. According to process engineer Kim Nelson, Senior Director, Strategic Consulting, at CRB, automation can go a long way to facilitate cell therapy manufacture. There is just one problem – integrated off-the-shelf automated systems don't yet exist. We catch up with Nelson to find out his thoughts on the conundrum and the future of the field.

How did you get involved with cell therapy process engineering?

At university, I obtained degrees in chemical engineering and biochemistry/biophysics – and I became very interested in biomedical and bioprocess engineering. In grad school, I studied cancer chemotherapy mathematical modeling. For a while, I taught at university, and then I had the opportunity to move into industry to work with cell culture process development – mainly working with anchorage-dependent cell lines and large-scale production on microcarriers. Cell culture tied in well with my graduate work and it was the 80s – a great time to join the industry, which was seeing a real blossoming of vaccine scale up and production, as well as recombinant work. Some years later, I moved to the engineering industry, where I was thrilled to be able to work with a range of projects and technologies. I've never looked back. Today, I mainly work with process engineering for cell therapies, and gene vector production.

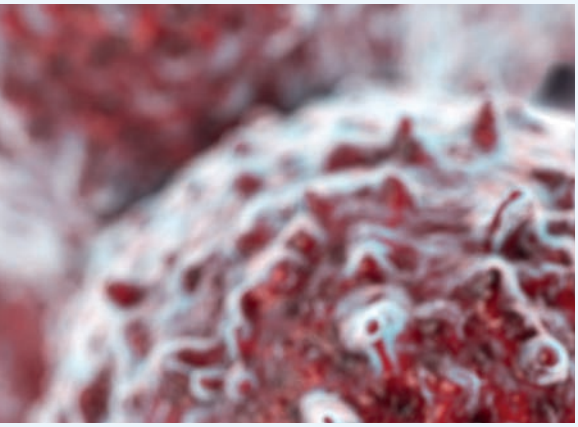
What trends have caught your eye in the cell therapy field?

I am fascinated by advances in immunotherapies – partly because of my original interest in cancer chemotherapy. Immunotherapies potentially hold awesome therapeutic power, but they also raise many challenges in terms of scale up and commercialization. Producing therapies for a small number of clinical patients is very different to handling a high-throughput situation, which is what many companies struggle with. They may understand the science, clinical importance, and biology of their product, but translating that into a high-throughput system – one that is also commercially sustainable – is daunting. Smaller companies are especially challenged because they often don't have the resources to staff the large and protracted development program that is needed to get a high-throughput system in place.

One of the biggest issues for the field is the fact that there aren't many commercial systems available. There has been an explosion in the number of equipment suppliers moving into the field, but most offer systems that are more appropriate for clinical scale operations. Many offer closed processing (closed processing systems have been very successful) for individual steps, but there isn't a truly integrated, high-throughput option available. Indeed, many of today's options aren't amenable to true automation – such as being able to introduce an apheresis bag, attach it, process the cells, incubate the cells, harvest the cells, wash the cells and then dispense them into the delivery bag ready to be frozen – all with minimal or no operator intervention. In most cell or gene therapy processes today, human workers perform the manipulations manually. The field could perhaps benefit from funding, such as from the NIH or other organizations, to develop integrated automation for different types of cell therapy systems.

What are the main challenges in terms of scale up?

From a process Quality-by-Design standpoint, characterization and identifying the critical quality attributes and critical process parameters that will translate to clinical outcomes is crucial. This is also the first step when moving to any type of manufacture and scaling it up. You need to understand the scale that you will



need, and you also need to be able to work backwards (scale-down) to determine the appropriate working ranges. One example might be large-scale cultures of anchorage-dependent allogeneic cells in a microcarrier bioreactor system. You need to understand the total number of doses of cells you'll need at market launch and the production growth, as well as the dose size. These will establish the throughput required, which then must be balanced between the number and size of the bioreactors. While this might be simpler at small scale, you can't do all of the process dependent and early clinical work in static culture systems like cell factories, Hyperflasks or Hyperstacks – you need to use a scaleable bioreactor system relevant to the required commercial scale; in this case, microcarriers or perhaps a packed bed type bioreactor. Along the way, you also need to be investing in process development – don't wait until things have moved too far along! Investing in the reliability, robustness, and repeatability of the process is very important. Automation can help by reducing operator interventions – thereby reducing the risk of errors and variability that occurs from one operator to another, as well as processing speed.

What are your top tips for scale up success?

Process definition and process development need to be a significant focus much earlier than companies realize. On many occasions, I have seen companies designing manufacturing facilities before they even have a defined process – key questions have not been asked and parameters have not been identified. In some cases, companies won't even know the critical quality attributes, let alone the critical process parameters. If it is a company's first product, they will need a good team to acquire the right knowledge. When it comes to a second similar product, it will be a little easier as some of the same parameters can be used as starting points – particularly if the company is working with a platform-type system. Start early, identify those critical quality attributes and the critical process parameters early, and select a scalable process – this information will improve your chances of success when it comes to scaling up to commercial manufacture. Without the right information, you'll often end up "over designing" a facility or a process, increasing the project costs and the risk of a delayed launch.

Cost is always a significant pressure in today's industry – how important is this for cell therapies?

Cost drivers for cellular therapies or other advanced therapeutic medicinal products are highly dependent on raw material costs, with media and growth factors being quite expensive and laborious. There are also fixed costs such as the facility and equipment costs to consider as well. The labor portion is particularly high for autologous therapies, where each patient's cells are a separate batch, and the processes have many operator manipulations and incubation steps. It takes time to develop a more economical process. And once a product is approved there is always the time, effort and cost of getting regulatory approval. When Dendreon first launched their cell therapy manufacturing operations, the cost of manufacture was high, but more efficient operations and cost-effective materials have helped bring costs down significantly.

Getting the manufacturing cost per patient dose into a reasonable range is crucial for the sustainability of the field – and healthcare overall. There's been much discussion about the pricing of the Novartis CAR-T product, Kymriah, and it seems as if Novartis will roll out an outcomes-based pricing model where payment is only required if the patient responds by the end of the first month after the therapy is administered. It's possible that more therapies will follow this payment model in the future, but although it may suit some countries, it won't suit all. Companies will still need to optimize their manufacturing costs and consider the final price of their product, particularly if they want to reach the widest possible range of patients.

Given the challenges that lie ahead, what are your thoughts on the future of the field?

Certainly there are challenges that must be faced in terms of manufacturing, but when it comes to treating disease I have a very hopeful outlook. Back in the 70s, there were dreams that cancer could be cured relatively easily with the knowledge that was being gained – and today's immunotherapies offer real potential for achieving remission or total cures for certain cancer patients, rather than just extending life for a short time. I am very optimistic. And it's not just cell and gene therapies that are making a mark on patient outcomes – there are many stem cell therapies in development which could have huge impacts in the biopharma space. Some will be major blockbusters, but others are for niche indications. In all of the cases where cells are the product, cost of manufacturing will be an issue, and automation of the operations has the potential to provide more robust, repeatable manufacturing, while reducing the facility and labor portions of the manufacturing costs equation. It's actually fantastic to see so many niche products being pursued. Providing the industry can solve the manufacturing challenges – and tackle costs – there will be many more promising treatments available in the coming years.

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

A Foggy Forecast?

What does your product demand guesstimate look like? Blue skies ahead? Heavy thunderstorms? More importantly, how can you be sure that the winds won't suddenly change?

By Michael Lehmann, President, Global Sales & Marketing, Pharmaceutical Services, at Thermo Fisher Scientific, Durham, NC, USA.

I was very interested to read Stephanie Sutton's editorial comment, "Bringing Down the House" in the June issue of The Medicine Maker (1). The editorial points out the challenges that pharma and biotech companies of all sizes face when it comes to forecasting demand for products. Some inaccurate forecasts have resulted in manufacturing plants being built, then standing idle, and eventually being demolished without ever producing a single dose, such as Sanofi's Montpellier facility in France. What an incredible waste of time, talent and resources that could be directed to new drug development.

The pharma industry is facing unprecedented challenges. Payers are demanding lower cost drugs, and yet the cost of getting a drug from discovery through to market approval is increasing – now estimated at $2.6 billion (2). In addition, a delay in launch is estimated to cost an average of $15 million per drug, per day. And research shows that a blockbuster drug will lose $1 billion in revenue annually until capacity is developed to meet demand (3). So whether you over-estimate or under-estimate demand, there will always be costs involved.

Unfortunately, the problem is not easily solved. Forecasting demand, particularly for a product launch, is mired in uncertainty. Each new drug's success is susceptible to variations in the external environment, the uncertainty of drug development, and the unpredictable actions of competitors. It is not unusual for forecast and actual dosage to vary by a factor of three – and getting it wrong could mean foregoing profit or tying up capital unproductively, and can be catastrophic for a small company without a financial safety net. The impact of inaccurate forecasting is perhaps greatest for large molecules because of

"Forecasting demand, particularly for a product launch, is mired in uncertainty."

"The outsourcing market is very mature – and often quick to adopt the newest technologies."

the cost of goods and the time it takes to access capacity; a biologics plant usually takes longer to construct than a small molecule plant – and build time pushes the biologics forecast windows out so far that you sometimes need to make a call on whether to build (or not) based on very early clinical data.

Instead of trying to make better predictions (which by their very nature will never be wholly accurate nor able to remove risk), I believe that biopharma companies would do well to consider alternative strategies that minimize risk. Historic approaches – building plants, for example – won't always work given the dynamic nature of the modern pharmaceutical landscape. And perhaps there is no reason for everyone to build proprietary plants when there are so many outsourcing specialists available, particularly for companies that don't have the resources or those that are concerned about forecasting. The outsourcing market is very mature – and often quick to adopt the newest technologies.

In my view, every decision should take into account the fact that patients are waiting – there is huge demand for new medicines at the right price. If the old ways of doing drug development aren't compatible with today's dynamic pharma landscape, we need to look for a fresh approach. And wasting money on facilities built for the wrong demand is not an option.

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Lead by the Nose

The nose is not just an anatomical region for locally-acting drugs – it is an open door offering rapid access to different organs

By Alain Regard, Technology Product Manager, and Pascale Farjas, Global Category Manager – Ear, Nose, Throat, both at Nemera, France.

When considering drug delivery, the oral and injectable routes are perhaps the most well used and well discussed, but many interesting advances are being seen in the nasal drug delivery field that should not be overlooked. The main advantages associated with the nasal route are ease of use, direct access into the bloodstream, rapid onset of action, and avoidance of hepatic first-pass metabolism, to name just a few. The nasal mucosa's proximity to the brain has also fuelled much interest in potentially using the nasal route to deliver drugs to the brain, although in practice this has proved challenging.

Despite the benefits of the nasal route, it is not well used for commercial pharma products. One of the reasons is perhaps the complexity of development – developing a new drug molecule is challenging enough, and using the nasal route also requires the design of an effective and patient-centric delivery device. Different studies have demonstrated that the device plays an important role in drug efficacy, as well as market success, and, overall, nasal drug delivery devices are well established and accepted by patients. A good device should be easy to use for everyone – healthcare professionals and patients. The device-user interface is a key element of the device development and human factor studies are crucial to ensure a device is intuitive and comfortable to use. Advances in devices and electronics are also opening up the possibility of adding features to increase patient safety and adherence, such as a "do not forget me" function.

With increasing competition in the pharma market today, the nasal cavity is worth exploring to differentiate drugs, or to refresh existing drugs with a new delivery method. On the locally-acting drugs side, several corticosteroid nasal drugs have recently (or will soon) come off patent, providing opportunities for generics companies. Vaccines are another good application for nasal sprays; for example, MedImmune's FluMist is sprayed into the nose to help protect against influenza. One of the most popular indications for nasal drug delivery, however, is pain management, and a number of approved medicines are already on the market, such as the Sumatriptan nasal spray for treating migraine headaches. In recent years, nasal drug delivery devices have improved their capabilities to target anatomical regions of interest for improving drug efficacy and pain relief. For instance, Optinose has developed an innovative concept for nasal aerosol delivery, using mouth exhalation to protect the lungs against particle penetration. Performance of nebulizer systems has also improved with mesh technology to target sinuses and chronic rhinosinusitis patients.

I see no reason why the nasal route shouldn't see increased future use in hospital treatments, such as following an operation, breakthrough pain associated with cancer, or multiple sclerosis. In fact, more and more nasal sprays are being developed for emergency use because of their fast absorption and onset of action; for example, nasal sprays have been developed for treating opioid overdose, anaphylaxis, and cardiac arrest.

One intriguing area of development is the delivery of drugs into the brain via the nasal cavity to treat central nervous system conditions. Nose-to-brain drug delivery has seen significant research during the last decade, but no real nose-to-brain proof of concept for humans has been realized. Many studies in animals claim direct nose-to-brain transport along the olfactory and trigeminal nerves, but the animal olfactory zone is more developed and does not prove human efficiency. Some clinical trials in man have suggested the potential of reaching the brain through nasal drug delivery, but definitive proof is lacking. However, this is a vibrant area of fascinating research, particularly for Alzheimer's and Parkinson's.

Despite the challenges, I am confident that the industry will see more nasal sprays reaching the market in the future. Nasal delivery is a fascinating area full of potential. Some of the projects I have noted recently include clinical research on intranasal octreotide to treat acromegaly and neuroendocrine tumors (1); using shark antibodies to cross the blood-brain barrier (2); and nose to brain drug delivery of Oxytocin in autism patients (3). Those with a nose for new drug development opportunities should not ignore the nasal route!

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They Shoot Horses, Don't They?

Age-based stereotypes exist, even in scientific communities. But is age related to research productivity – and, if so, to what extent?

By Victoria F. Samanidou, Laboratory of Analytical Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, Greece.

The relationship between age and productivity is not a simple one to quantify. Older workers are assumed to be less effective and industrious than their younger colleagues when it comes to more physical tasks (1)(2). But what about science in particular?

In scientific communities, opinions on the net effect of age on productivity are varied. Several factors influence the productivity rate of researchers or academics; experience, health status, position, rank, and many more. It also begs the questions: what exactly is "productivity" and how do we measure it? In academic communities, it is often measured by the number of publications, along with the number of self-excluded citations and the h-index; the former relating to quantity and the latter to the quality and impact of the work. Do older scientists publish less or more? It is difficult to make an estimation – the determinants of individual productivity are extremely complex and I doubt whether typical metrics are in any way useful. However, I can say that authorship is not always directly related to actual productivity.

Perhaps rather than trying to guess the productivity of individuals, it is more useful to reflect on the "typical" path in a scientist's career. In short, it can take a long time to get to the top. On the path to recognition, I have witnessed three typical turning points in the career of academics; the first occurs at around the age of 35-40 years, where researchers are expected to step up their productivity to reach a higher position. A second inflection point comes at the age of 50-55, when the rate of productivity can reach a plateau or decrease slightly (3).

The third turning point, I believe, comes when researchers are approaching retirement age. As researchers move up the stratified hierarchy of science, recognition reaches a peak, leading to collaboration with more productive groups, greater success in gaining access to funding and more likely publication in scientific journals with a higher impact – all boosting perceived productivity. However, there is another trend in this age bracket; older professors publish far fewer first-authored papers and instead move to the end of the list of co-authors, as they are more likely to be the leaders of their own groups.

No one can deny that with time, physical power decreases. In addition, technological developments and innovations are not always easily integrated by older scientists. On the other hand, a significant number of older scientists stay active in research, keep their productivity at a high level until their retirement, and continue to inspire the young, still playing an effective role in the production of high-impact papers. Indeed, if one is able to inspire 10 or more team members to be more efficient (while striving for high quality), the overall effect is an increase in productivity for the group, which perhaps far outweighs the potential of a single individual.

So are older scientists more productive than their younger peers? I would argue that the most important aspect, whatever the age of the scientist, is the degree of satisfaction that they gain from collaboration with others – and, even more important, their passion for furthering research. And I don't believe either of those aspects have anything to do with how old you are. There are more than a few examples of scientists – young and old – who have simply lost interest; they require a change in attitude or should consider an alternative profession...

All scientific research relies on collaboration – and so researchers of all ages need to play a significant role in its dynamic. With understanding on both sides, it's a multi-way process; when we are surrounded by young people – eager students in academia or dynamic young scientists in research institutes or industry – it can be easier for us to maintain a "youthful" outlook; in turn, younger colleagues can benefit from the great experience, knowledge and tenacity of their superiors. To my mind, when it comes to age, it's less of a generation "gap" and more of a spectrum.

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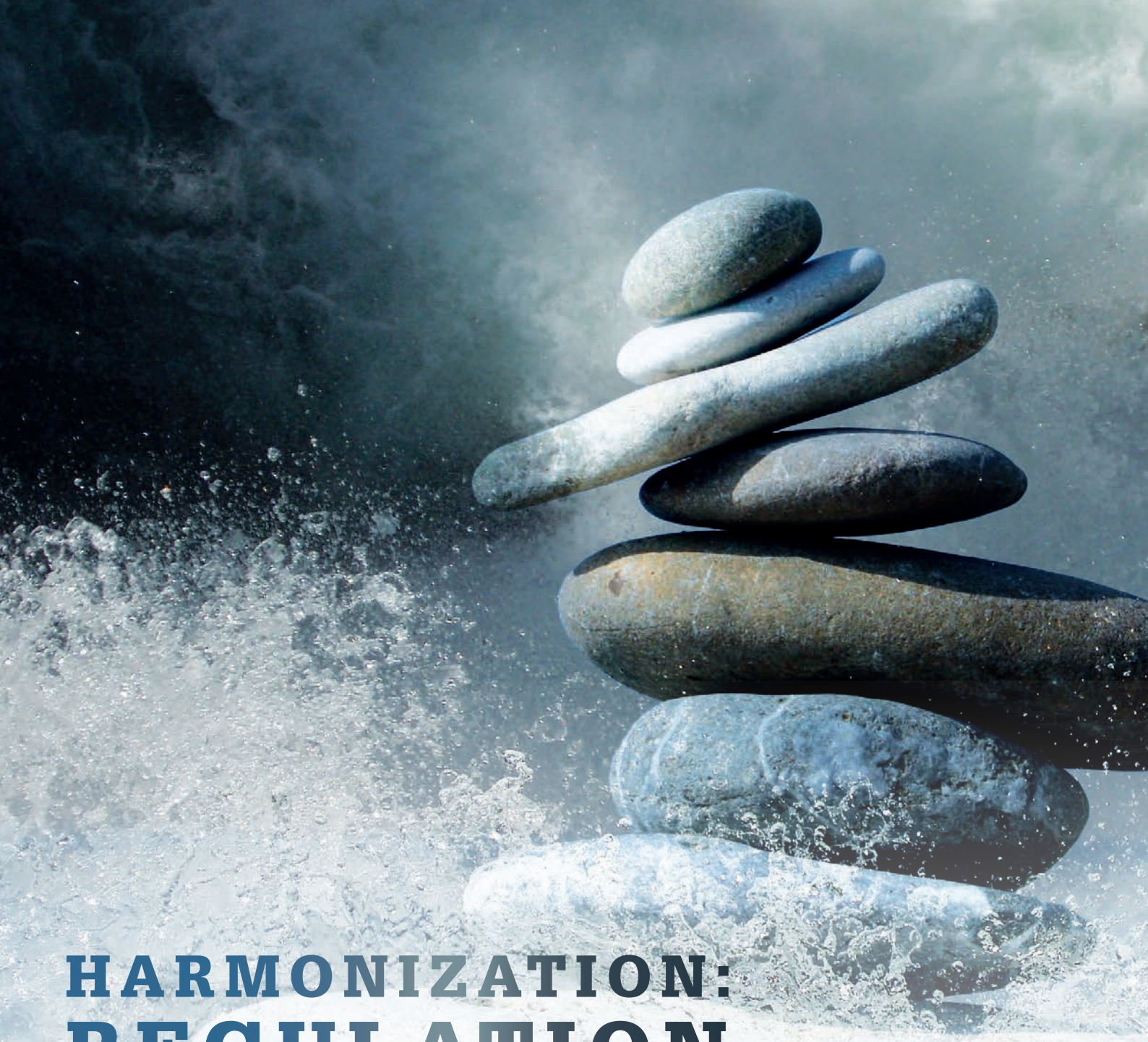

HARMONIZATION: REGULATION GOES GLOBAL

With globalization creating opportunities for companies but causing havoc for regulators, an industrywide demand for regulatory harmony has arisen. But who benefits? And how will the picture look in the years to come? We survey pharma's global regulatory landscape.

By James Strachan

Globalization is a hugely disruptive force. Increasing access to the world's economies since the 1980s has created winners and losers – with recent political upheavals in the UK and US sometimes viewed as reactions against policies of free-flowing labor and capital.

But on the face of it, globalization has already happened. In almost every industry, supply chains are deeply interwoven, with products sold in one country made up of components supplied from every corner of the world. Pharma is really no different: 40 percent of drugs sold in the US are manufactured abroad, as are around 80 percent of active pharmaceutical ingredients (APIs) (1). National regulators are now no longer able to make sure the products on their markets are safe, efficacious and manufactured in accordance with prescribed quality standards, without giving thought to the wider world. As the nature of industry has evolved, the need for a global view of regulatory oversight has arisen (as former FDA Commissioner, Margaret Hamburg, discusses on page 23).

Surveying the regulatory landscape 50 years ago, one would find a system of largely independent and divergent pharmaceutical systems, with individual countries working separately to strengthen their regulatory capacities. Today's system is characterized by increasing levels of harmonization – from collaboration on selected topics, to Mutual Recognition Agreements (MRAs), all the way to full integration, as with the European Union. Key pillars of the new regulatory landscape are global bodies, such as the World Health Organization (WHO) and the International Council for Harmonization (ICH), which work to achieve global scientific consensus in developing regulatory guidelines.

Globalization raises many questions. Who benefits from increasing harmonization of pharma regulations? Does the industry want more? How important are the global bodies? And how will the regulatory landscape look in the coming decades?

Why harmonize?

Joel Lexchin, Professor Emeritus in the School of Health Policy and Management at York University, Canada, and an emergency physician at the University Health Network in Toronto, believes that the main driving force behind harmonization in the pharmaceutical industry is finance. "The industry isn't interested in having to produce multiple different dossiers for each regulatory environment. Even if you don't have to repeat trials, there's still the cost of putting together information in different formats. Industry benefits from being able to get its marketing applications in quicker, allowing it to retain more patent life and thus return on investment."

Whether this necessarily increases value for the patient is a separate and more complicated question, but the example of the Japanese "drug lag" is one demonstration of how regulatory divergence leads to delayed access to medicines. Pierre-Louis Lezotre, Vice President, Global Regulatory Affairs at Avanir Pharmaceuticals, points out, "It used to be the case that Japanese patients waited, on average, three years after approval in Europe or the US to have access to a new medicine."

"Industry benefits from being able to get its marketing applications in quicker, allowing it to retain more patent life and, thus, return on investment."

In the mid-2000s, the Japanese Ministry for Health, Labour and Welfare began putting in place measures to cut the time lag (2). As Lezotre explains in his book "International Cooperation, Convergence and Harmonization of Pharmaceutical Regulations: A Global Perspective," in an effort to resolve the drug lag, the PDMA (Japan's Pharmaceutical and Medical Devices Agency) launched its "International Strategic Plan" for bilateral, regional and global cooperation, and established an internal office in charge of international affairs. The plan involved hiring more staff and introducing an "innovation premium," as well as establishing a special committee to review pharmaceuticals approved elsewhere in the world and to recommend fast-tracking, where appropriate, in Japan. In 2008 and for the first time, the PMDA agreed to consider data from global clinical trials in all drug applications – as long as safety studies included Japanese patients. Then, in 2011, the PMDA began offering sponsors a regulatory strategy consultation earlier in drug development. Japan also entered into a Good Manufacturing Practice (GMP) MRA with the EU in 2012, which is set to increase in scope this year (3).

Combined, these factors have helped Japan to significantly cut its drug lag (2). "We're talking about access to life saving medicines," says Lezotre. "Increasing that access can only be beneficial for patients."

Another key patient benefit is more effective pharmacovigilance as a result of international cooperation. Signal detection refers to information on a possible causal relationship between an adverse event and a drug – the relationship being unknown or incompletely documented previously. Lezotre explains, "Sharing data among different countries is crucial to being able to

"The WHO is well known for its work in vaccines and combating pandemics, but it has also played a significant role in harmonization."

improve signal detection and act quickly if there's a problem. We need international agreements on rapid data sharing, as well as harmonized standards so that the various databases can talk to each other. Such activities are hugely important to keep patients safe."

State of play

Just how harmonized are pharmaceutical regulations today? According to Lezotre, international cooperation, convergence of pharmaceutical regulations and harmonization of standards are already a reality. This phenomenon has grown in importance over the past several decades, through three main types of harmonization initiatives: bilateral, regional and global. Bilateral agreements are between two countries, or between one country and a group of countries. One good example is the EU and Israel's Agreement on Conformity Assessment and Acceptance of Industrial Products. Here, Israel adopts and implements relevant EU law to "extend certain benefits of the internal market."

For example, in return for adopting EU standards, Israel benefits from the EU recognizing its industrial standards as equivalent – with GMP Certificates, manufacturing and import authorizations, and certification of conformity of each batch, issued by either party being mutually recognized. This means fewer "non-tariff barriers" to pharma trade, such as divergent standards and customs checks. The agreement covers "medicinal products, active pharmaceutical ingredients, pharmaceutical excipients or mixtures thereof, for human or veterinary use [...] chemical and biological pharmaceuticals, immunologicals, radiopharmaceuticals, and herbal medicinal products" (4).

Another example of bilateral cooperation is the long history of collaboration and harmonization between the EU and the US. In April 2007, the EU and the US signed the Framework for Advancing Transatlantic Economic Integration between the two regions, which specifically called for the promotion of "administrative simplification in the application of regulation of medicinal products." This move was followed up with a Medicines Regulation Transatlantic Administrative Simplification Action Plan, published in June 2008, which promoted cooperation in inspections, biomarkers, counterfeit medicines, risk management, scientific advice, biosimilars, pediatrics, and advances therapies (5). These initiatives have become standard practice for the EU and the US, with further collaboration on pharmacovigilance, orphan drug development, and inspections – the latter culminating in an MRA earlier this year (6).

The second type of harmonization initiative is regional. The best known example is the EU, but there are a growing number of additional groupings, including the Pan-American Network for Drug Regulatory Harmonization (PANDRH), the Gulf Cooperation Council (GCC), the Southern African Development Community (SADC), the Association of Southeast Asian Nations (ASEAN), and Asia-Pacific Economic Cooperation (APEC). If we take APEC as an example, its Life Sciences Innovation Forum has managed to coordinate multicountry clinical trials, the implementation of good clinical practices, efforts to combat counterfeit medicines, and more. By 2020, APEC is seeking to "achieve convergence on regulatory approval procedures" (7).

The final and increasingly important harmonization initiative is global – involving many organizations and countries. The two major examples are the WHO and the ICH. "The WHO is well known for its work in vaccines and combating pandemics, but it has also played a significant role in harmonization," says Lezotre. For example, the internationally accepted classification system for drugs – Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) – was driven by the WHO, after recognizing the need for an international standard for drug utilization studies (8).

The WHO has also been instrumental in improving access to medicines in the developing world, where Drug Regulatory Authorities lack the resources and expertise to carry out all functions (9). Instead of relying on the decisions of regulators in the developed world, the WHO launched its own prequalification program, which includes a team of assessors made up of WHO staff and experts from National Regulatory Authorities (NRAs), who evaluate data presented by medicine makers. A team of inspectors then verifies the manufacturing sites for the finished pharmaceutical product and confirms its APIs comply with WHO good manufacturing practices. Once a decision is made, the medicine appears on the WHO's list of prequalified medicines and can be purchased by international procurement agencies – for example, UNICEF, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and UNITAID – for distribution in resource-limited countries. Traditionally, WHO prequalification focused on only a few diseases (in particular, HIV, malaria, and TB), with the

A View From the Top

Margaret Hamburg served as FDA Commissioner from May 2009 to April 2015, and led the agency through a period of increasing globalization.

What were the main challenges you faced as a result of globalization?

Finding out just how much of our food and medicine either comes from overseas, or is composed of elements from overseas, was a revelation. We needed to find a way of ensuring the quality of the products coming in, as well as the integrity of the supply chain. In the past, goods could be checked for quality at the border, but, with the dramatic increase in volumes, that just isn't practical today. We had to oversee an increasing number of players in a complex supply chain, with many products coming from countries where the regulatory infrastructure is much less mature than in the US or the EU.

How did you go about tackling the problem?

The scale of the problem and the workload involved was enormous. There were literally tens of thousands of facilities that we needed to inspect; in an era of constrained resources, and with new increasingly complex products, it was a challenge that required new solutions. The first thing we had to do was become much more global in terms of our reach, which meant increasing the number of FDA offices worldwide and building our capacity to do site inspections overseas – working with companies and other regulatory authorities.

How important was collaboration?

Well, we weren't the only agency faced with this problem. Countries across the developed world were thinking about how to deal with globalization and products coming from a wide range of countries. Building bilateral relationships with those countries – sharing information more effectively – was important. We needed to think about how to better harmonize systems of inspections and approaches to approvals so that different regulatory agencies could share workloads. It seemed crazy to me that you could have FDA inspectors going into a plant, followed by EMA inspectors, followed by Health Canada, and so on. And yet other facilities would go unvisited for prolonged periods of time.

Our aim was to find ways to pool our resources to work better as regulators, and to also decrease unnecessary burdens on companies that have to deal with different serial inspections, each with different requirements and expectations.

Working within systems of international collaboration was also very important: the ICH and WHO being two examples, as well as the Pharmaceutical Inspection Co-operation Scheme (PIC/S), which we joined while I was commissioner. It was clear to me that we had to approach global collaboration in a much more organized way, so we began building on some of the initiatives that were already in place, as well as trying to extend and clarify those activities.

We also undertook an effort to create an umbrella organization, the International Coalition of Medicines Regulatory Authorities (ICMRA), to oversee/coordinate the activities of the ICH, PIC/S and some of the other initiatives, to make sure we were covering the necessary landscape and that there wasn't duplication of efforts. There were critical issues that needed to be addressed, such as information sharing and the question of how to align different national regulatory authorities when every country has their own national laws and standards. Greater integration and more information flow is key to allowing national regulatory authorities to do their jobs in a globalized world.

You can read more from Margaret Hamburg in the November issue of The Medicine Maker.

majority of approved products being generic HIV drugs. However, in May this year, the WHO launched a new pilot project for prequalifying biosimilar medicines (10).

The WHO also works with the World Bank and NGOs to finance harmonization projects worldwide. "The World Bank manages a trust fund with money from the Gates Foundation, the UK Department for International Development, and the US Government, to finance regional harmonization projects under the African Medicines Regulatory Harmonization Initiative," says Andreas Seiter, Senior Health Specialist at the World Bank. "We work in partnership with the WHO, NEPAD and others to help regional groups in Africa (EAC and ECOWAS) implement projects that lead to joint assessments, harmonized requirements, joint GMP inspections, and so on."

The WHO also promotes harmonization in a number of other ways; for example, the International Pharmacopoeia (Ph.Int.) comprises a collection of quality specifications for pharmaceutical substances, which has legal status whenever a national or regional authority introduces it into appropriate legislation. The WHO has also developed standards for pharmacovigilance through its WHO Program for International Monitoring, launched a certification scheme on the quality of pharmaceutical products, and established international biological reference materials – to name but a few initiatives.

The WHO also spawned what is arguably the most important global harmonization initiative: the ICH.

The ICH

In 1989, Paris hosted the WHO Conference of Drug Regulatory Authorities, where discussions took place on the possibilities for greater harmonization between the European Economic Community, Japan, and the US. Soon afterwards, the big three approached the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) to discuss a joint regulatory-industry initiative (11) – this became the ICH, which was officially born in April 1990 at a meeting hosted by the European Federation of Pharmaceutical Industries and Associations in Brussels.

David Jefferys, Senior Vice President for Global Regulatory, Healthcare Policy and Corporate Affairs for Eisai Europe, Chairman of Eisai's Global Regulatory Council and former joint Chief Executive of the UK's MHRA, was involved in setting up the ICH. "It's fascinating to see how things have changed over the years, but the original idea was that it simply did not make sense to be doing things so differently across the regions – it still doesn't," he says.

Since 1990, the ICH has expanded to include more than the initial three regulatory and industry members, such as "standing" regulatory members from Canada and Switzerland; three additional regulatory members from Brazil, China and South Korea; as well as additional industry members (the Biotechnology Innovation Organization, the International Generic and Biosimilar Medicines Association, and the World Self-medication industry). There are also 23 observers, which include international organizations, such as the IFPMA and the WHO, regional initiatives, and several NRAs – including those from Australia and India. Regulatory members have the right to vote in assembly and appoint experts in Working Groups, and are expected to implement ICH Guidelines in accordance with the applicable "Rules of Procedures." Observers do not have voting rights, but can nominate delegates to attend assembly meetings, and appoint experts in working groups following a positive decision of the management committee (12).

"The ICH started with the three regions, but has evolved over the years to include more NRAs and regional groupings – becoming a big part of the global pharmaceutical harmonization scheme, and producing some highly significant standards," says Lezotre.

Until relatively recently, significant differences existed between countries and regions in terms of non-clinical development regulations. "There were discrepancies in the species and number of animals required, the type of study, and so on," says Lezotre. "If you wanted to develop a drug that could be marketed worldwide then you had to do various additional studies – with an increasing number of animals." The ICH's M3 (R2) guideline on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals (together with several other key ICH non-clinical guidelines) harmonized many aspects of non-clinical development (13). These guidelines have been adopted in the EU, Japan, the US, Canada and Switzerland.

The ICH has also been instrumental in the creation of the eCTD (electronic Common Technical Document). The CTD is a set of guidelines for the submission of a regulatory dossier to obtain marketing approval for a new drug or a variation to the licensing of an existing drug. Prior to implementation of the ICH's CTD in 2002, the EU, Japan and the US had their own set of guidelines, creating significant administrative burdens for drugmakers. Two years later, the ICH finalized an electronic version of the CTD, which was implemented in all ICH regions. "This is very important," says Lezotre. "This additional step wasn't about harmonizing the content of applications, but rather the structure of the information provided. The objective was to organize information electronically in the same way, using the same format. Having the same structure and terminology not only reduce delay in reformatting but also facilitate exchange of data between regulators."

A study from 2012 surveying companies that had implemented an eCTD found that "more than three-quarters of individuals with eCTD experience were able to shorten their total time to approval, and more than 90 percent of this group was able to demonstrate cost savings relative to paper submissions, regardless of their company kind, size, or number of submissions," according to the authors (14).

"The time savings arising from the eCTD are amplified because they are harmonized across the ICH regions," says Jefferys. "Any measure that means you don't have to expend additional resources is a plus."

"The ICH has also standardized medical terminology with MedDRA, which was a key achievement," adds Lezotre. "When you carry out a clinical study, the study report is based upon terminology. And if you want to share information internationally, you need a standardized dictionary."

The ICH has also been instrumental in the harmonization of Good Manufacturing Practice (GMP) and pharmacovigilance activities. "The ICH now allows for common development of products. It makes it much easier for products to be accepted, with common dossiers, paperwork and reporting arrangements for pharmacovigilance, as well as guidance on inspection criteria, and so on," says Jefferys. "The ICH has become a bedrock for the pharmaceutical industry."

In perfect harmony

When discussing the harmonization of medicine regulations, it's important to consider what actually happens when countries have divergent standards. Does the global standard tend to converge on the highest existing standards, the lowest standards, or somewhere in between?

The Long Road to Perfect Harmony

We have discussed how globalization has led to increasing regulatory harmonization – with global bodies such as the ICH playing an important role in that process. However, in certain areas, there is significant disharmony across the ICH regions. Hisashi Urushihara, Professor in the Division of Drug Development and Regulatory Science at Keio University, Tokyo, Japan, looked specifically at the differences in ethical standards for pharmacovigilance studies between Japan, the US and the EU, and found disharmony and inefficiency caused by a lack of international standards (1).

What were your main results?

We found that the requirements for obtaining informed consent in phase IV observational studies differed across the three regions, or were not well defined – especially in Japan and the US. Having to satisfy the different and/or arbitrary requirements for informed consent must have wasted an enormous amount of limited time, resources and money. For example, we found that studies with the same purpose were often replicated among different regions without considering data integration due to high hurdles involved in meeting multiple national standards covering data integration and transfer, in order to derive a single result. There were also complex logistics involved in carrying out multi-regional studies, and study data wasn't being transferred.

What role does the ICH play in the regulation of post-marketing observational studies?

So far, the ICH has played a relatively small role in standardizing the planning and implementation of post-marketing observational studies when compared with pre-marketing – where we have seen how data sharing across regions is based upon compliance to the same ethical standards. ICH E2 pharmacovigilance (clinical safety) guidelines, including E2A to E2F, mainly focus on the regulatory reporting of drug safety (except for the E2E guideline on pharmacovigilance planning). The 2004 E2E guideline is the sole guideline that describes the standards and policies in planning pharmacovigilance activities, but it only provides high-level policy regarding research ethics and compliance to applicable national ethical standards.

Is there a problem with international standards not being incorporated into legislative structures?

As we said in our paper, "without effective development and use of regulatory guidance for data quality and data sharing for regulatory-driven post-marketing observational studies, we may find that important collaborative research that could address rare safety events, and drug safety and effectiveness of subgroups, will be at best inefficient and at worst left undone."

We see that pharmaceutical companies, and sometimes regulatory agencies, do not always comply with or respect the ICH guidelines. This prevents opportunities to reduce duplication of activities related to drug development and safety.

How do we "bridge the gap" between the different ICH regions?

The ICH's Good Clinical Practice (GCP) renovation concept paper was issued in January this year, and offers a new perspective on observational studies, such as registries for regulatory decision making. The new GCP stipulates the standard policies and procedures for both interventional clinical trials and observational studies. We propose this revised GCP guideline be used to standardize the ethical and quality conduct of observational studies for the purpose of regulatory decision making.

Reference

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Lexchin argues that, in many cases, the ICH "harmonizes to the lowest common denominator." He refers to a 2002 study by John Abraham, which contended that the ICH's claims about the implications of technical harmonization were not valid, and that "within the ICH, a discourse of technological innovation and scientific progress has been used by regulatory agencies and prominent parts of the transnational pharmaceutical industry to legitimize the lowering and loosening of toxicological standards for drug testing" (15).

Lexchin believes the loosening of standards reflects the influence of the ICH's industry members, which he thinks has also manifested itself in other ways. "It's interesting to look at the areas the ICH does not get itself involved in," he says. "The ICH has not set standards around how patients should be recruited into clinical trials, and I don't believe it sets a mandate for the inclusion of women or other groups in clinical trials – which might make them more expensive for companies. It also hasn't entered into the realm of how promotion should be regulated, and I do not believe industry would want the ICH to start developing standards on promotion that are stricter than those currently imposed by national regulators."

Lezotre disagrees. "It stands to reason that if you have the very best experts from all over the world coming together to work on a technical question, the resulting standard will be of a higher quality than if it had been developed by the best experts in a single country," he says. "For the major critical topics, I do feel that we are harmonizing to the highest standards – you can't say we are developing lower standards than we were 40 years ago."

Trade and International Standards

There seems to be growing interest in the politics of trade and regulation. In the past few years, there have been protests over the Transatlantic Trade and Investment Partnership; Donald Trump threating to slap a 45 percent tariff on Chinese imports, and demanding two regulations be cut for every new one; and the Brexit vote, with some on the "Leave" side hoping that Brexit will bring new trade deals and a "bonfire of regulations."

But lurking under the surface – binding trade and regulation – is harmonization and the role of international standards bodies. Modern trade deals go beyond cutting tariffs (average global tariffs are already under three percent), with the real gains coming from the removal of non-tariff barriers to trade. Divergent regulatory systems are one such barrier, and their removal through the adoption of international standards features in many modern trade deals. Indeed, countries are obliged by the World Trade Organization's Technical Barriers to Trade Agreement to use relevant international standards "as a basis for their technical regulations."

Pharmaceutical regulations feature as part of this trend towards common standards, as revealed by a number of EU trade agreements. Looking at the EU-South Korea deal, Annex 2-D, Chapter Two reads, "The Parties will take into account, as appropriate, international provisions, practices and guidelines for pharmaceutical products or medical devices, including those developed by the WHO, the OECD, the ICH, the GHTF [Global Harmonization Task Force] and the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S)." The same paragraph also appears, nearly word for word, in the EU-Singapore Free Trade Agreement, and Japan has agreed to "refer to the ICH as the international standard-setting body and use ICH guidelines as [the] basis for its legislation" as part of an EU trade deal.

Beyond the EU, in the Trans-Pacific Partnership, Annex 8-C of the section on pharmaceuticals, reads: "The Parties shall seek to collaborate through relevant international initiatives, such as those aimed at harmonization, as well as regional initiatives that support those international initiatives, as appropriate, to improve the alignment of their respective regulations and regulatory activities for pharmaceutical products."

"If you want large volumes of goods moving from one country to another, you can't inspect everything at the border," says Lezotre. "The best way to make sure goods are safe and effective is to have common standards and agreements over inspections – this is why harmonization underpins modern trade deals."

But this may pose a problem for those hoping to deregulate and sign new trade deals simultaneously. If there is an agreement to harmonize standards as part of a trade deal, there's only a limited amount of deregulation possible before a deviation from agreed common standards.

Despite this, Lezotre would like to see a number of significant changes in the global regulatory landscape, including – as Lexchin also notes – representation of all stakeholders, such as doctors and patient advocacy groups, at the ICH.

Lezotre also believes there needs to be greater coordination of global harmonization initiatives. "We need to define the role of each initiative within an overall picture," he says. "There's still some duplication of work between the ICH and WHO. You also have regional groupings developing standards independently of the ICH – why not involve the ICH?"

The creation of an international medicines agency is another suggestion from Lezotre. "It would not be a new EMA or FDA – obviously you wouldn't have one agency approving all the drugs in the world. But an international agency could be at the head, facilitating cooperation between different initiatives and Drug Regulatory Agencies. It could also take on some specific projects, such as the global designation, development and regulation of orphan drugs," he says. "Could the ICH become this body? No, the ICH does not have the right legal structure. The new global agency would rely and build on the ICH, but I would differentiate their roles. This new International Medicines Agency could be a branch of WHO that would coordinate the global pharmaceutical system and manage the day-to-day business in line with the WHO strategy. The WHO has the legal basis and mandate for such an organization and is also well structured to represent developing countries in these discussions and projects."

Greater harmony on the horizon?

It's difficult to predict the global regulatory landscape of coming decades. Although the forces of globalization have driven greater harmonization, the future will depend largely on politics. "Few countries and international organizations see regulatory harmonization as a priority to which they must commit funding and capital," says Andreas Sieter. "Many regulatory agencies are inadequately staffed and funded, and lack the capacity to collaborate effectively in cross-border initiatives. Industry is also fragmented with various players benefiting from niches created by regulatory fragmentation. Some 'weaker players' will likely fight harmonization efforts because they tend to bring higher standards and more transparency, which benefits stronger, international manufacturers."

Lezotre asks, "Are we going to have leaders working for more cooperation? We've already seen a big shift between Obama and Trump in terms of cooperation with other countries. Will

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APEC continue to be supported? Will the changes happening in the gulf countries affect things? The political and economic facts are key to the question of whether or not pharma will become more harmonized."

Having said that, Lezotre does believe greater harmonization is inevitable. "Our leaders and regulatory authorities have a mandate to improve public health, and the best way to support global health is to support common high standards."

But will this mean an end to regional and bilateral agreements as international bodies grow in importance? "No, I don't think so," says Lezotre. "Global initiatives like the ICH and the WHO are becoming increasingly important, but they sit upon the system of regional and bilateral agreements. You can't have 195 countries in the room discussing the development of standards – there needs to be some organization." Lezotre argues that regional initiatives are key to relaying information from individual countries to the global level. "You also need to consider that there are countries out there with no regulatory system in place. You can't expect a country with one or two staff working on pharma regulation to have the capacity of the FDA; clearly, they can't participate in all the working groups at the global level, but their needs must be taken into account – this is why bilateral and regional initiatives are so important."

Jefferys also points to the increasing importance of regional alliances. "We're seeing greater cooperation in Africa and South East Asia, and I think we're going to see more mutual recognition type agreements and more workload sharing in the developing world," he says. "I think eventually we will see an African medicines agency."

Lexchin believes that regulatory harmonization is important, but hopes that the historical context of how different regulatory systems have developed is not lost. "In Europe, there's a tripartite model of regulation that involves industry, medical professions and government, which isn't the case in North America. I hope that harmonization does not override the cultural norms that have developed over the decades."

Lexchin is also concerned about the democratic accountability of international standards bodies, such as the ICH. "To be honest, I would have preferred to see the role of the ICH taken on by the WHO, which, despite its problems, remains a nominally democratic institution," he says. "If we are stuck with the ICH model, then I think it needs to go beyond its last reform – where all the relevant stakeholders have a voting role, including patient groups, consumer groups, professional bodies and developing countries." He also points out that the ICH has been criticized for developing standards that are more rigorous than actually required in certain cases to exclude generic manufacturing countries, and suggests that a more inclusive ICH might help.

Jefferys is pleased with developments in the ICH towards inclusivity, with the addition of countries such as China, South Korea, and Brazil, plus the various regional groupings that have joined as observers. He also agrees with Lexchin about the involvement of patients. "I was responsible for bringing patients into the precursor to the MHRA, and I do believe we will see patients on regulatory approval bodies and international standards initiatives, such as the ICH," he says. "How long will it take? I don't know, but I think it has to go in that direction."

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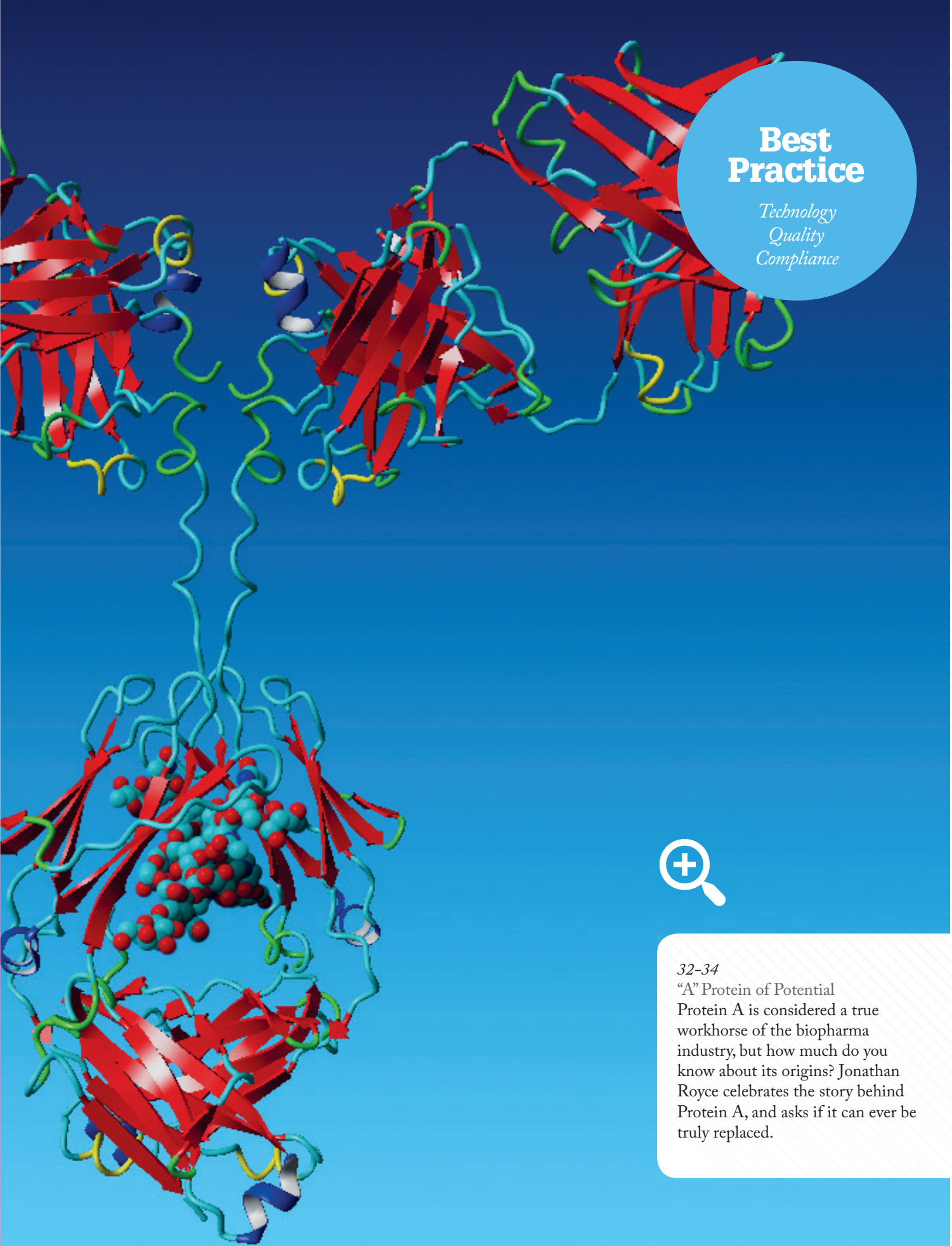
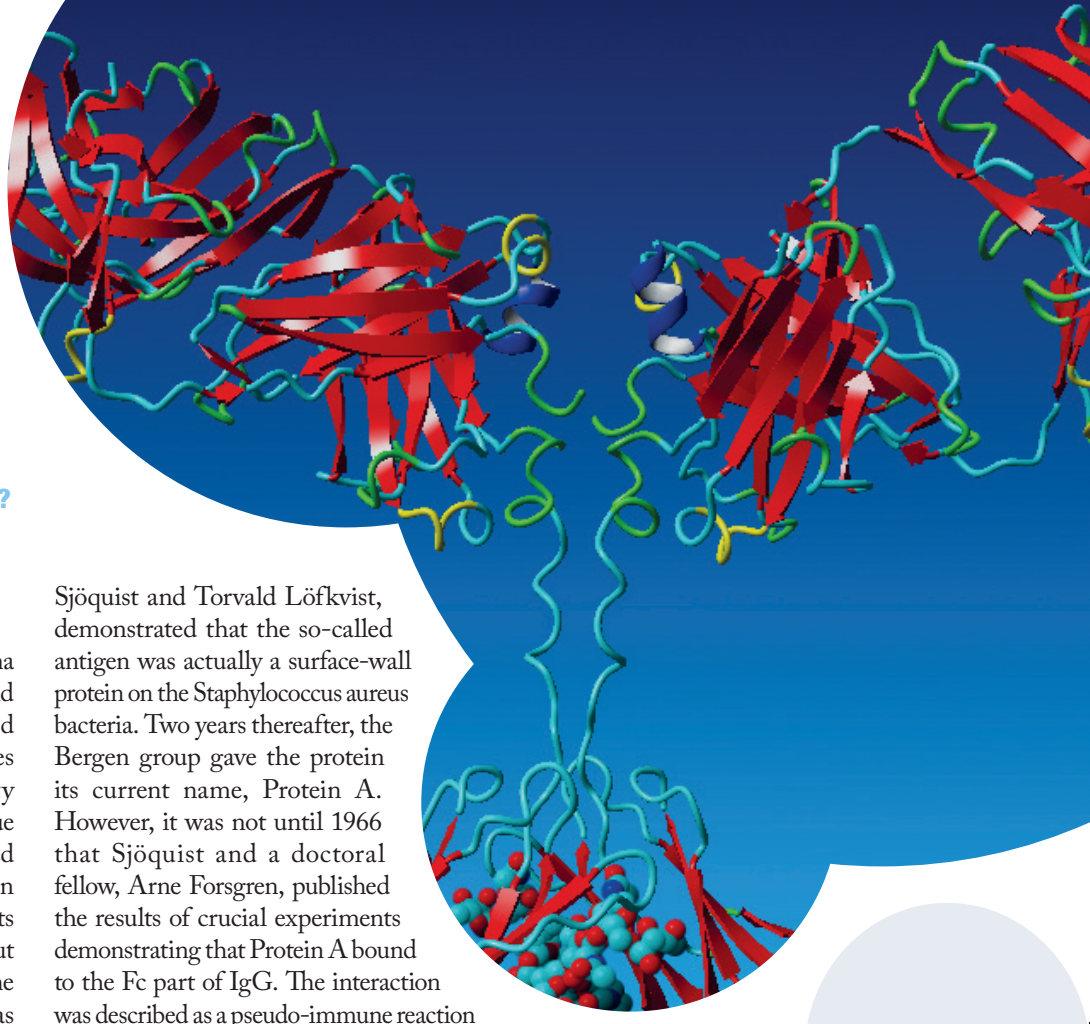




"A" Protein of Potential

Where would the biopharma industry be without Protein A? And can it ever be topped?

By Jonathan Royce

Protein A is a true workhorse of the pharma industry. It has been used for decades and is well established as the preferred method of purification for monoclonal antibodies because of the high yield and purity achieved in a single step (1). The technique is so common today that it is often referred to by its own acronym: "PAC" – Protein A chromatography (2), but most scientists today take Protein A for granted, without so much of a thought as to where it came from, or how much work the industry has put into refining and enhancing its abilities.

Looking back on the past techniques and technologies in one's industry is always fascinating. Protein A is naturally occurring and natural selection has bestowed it with high selectivity. It was first discovered in 1958 when Klaus Jensen at the University of Copenhagen reported the existence of an antigen associated with staphylococci that reacted with 500 types of normal human serum. He called this antigen "Antigen A". Four years later, two professors from the University of Umeå (Sweden), John Sjöquist and Torvald Löfkvist, demonstrated that the so-called antigen was actually a surface-wall protein on the Staphylococcus aureus bacteria. Two years thereafter, the Bergen group gave the protein its current name, Protein A. However, it was not until 1966 that Sjöquist and a doctoral fellow, Arne Forsgren, published the results of crucial experiments demonstrating that Protein A bound to the Fc part of IgG. The interaction was described as a pseudo-immune reaction and sparked a great deal of additional research on the microbiology, biochemistry and biological activity of the protein (3).

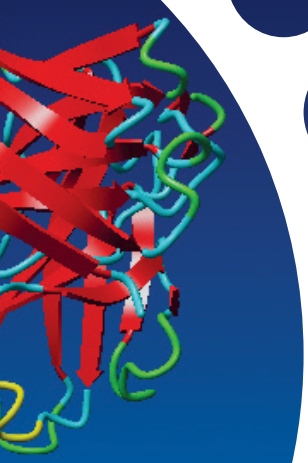
"Many researchers have attempted to replace the Protein A step with other technologies."

In the medical world, Protein A is the focus of much research on the virulence of S. aureus. The bacterium can cause skin and soft tissue infections, blood infections and subsequently heart infections. It is the cause of more than 20,000 deaths in the US alone each year, making it more fatal than influenza, viral hepatitis and HIV (4). Protein A plays a key role in the bacteria's ability to evade the human immune response; the binding of protein A to the immunoglobulins reduces the effectiveness of the B cell response, thereby interfering with the development of protective immunity (5). Protein A is also one of the von Willebrand factor (vWF) binding proteins on S. aureus, promoting the adhesion of staphylococcal cells to vWF-adsorbed surfaces, such as catheters (6). Most recently, Protein A has been shown to induce bacterial aggregation, which results in biofilm formation on host tissues and implanted medical devices (7).

The road to optimization

For the purposes of antibody purification, Protein A was not even considered as a functional ligand until 1972 (8). It took six more years before a Protein A resin was commercialized and it was not until 1986 that a therapeutic antibody was approved using protein A as a capture step in the purification process (9). Early versions of protein A were produced in the native host cell, S. aureus, which is challenging to produce at large scale due to its excretion of exotoxins. However, most modern versions of Protein A are produced recombinantly in E. coli or Brevibacillus.

From an industrial standpoint, one of the most important research efforts concerning Protein A was performed by Mathias Uhlén's laboratory at the KTH Royal Institute of Technology in Stockholm. Uhlén and colleagues demonstrated that by replacing all asparagine residues with other amino acids, one could dramatically improve



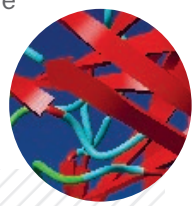
the chemical stability of Protein A towards alkaline conditions (10). The discovery enabled the replacement of expensive clean-in-place reagents (for example, 6M guanidine hydrochloride) whose use previously cost as much as the initial procurement of the chromatography resin itself (11). It also simplified process development activities by reducing the VH3 interaction with antibodies, thus enabling the use of a single elution pH for a range of antibodies (12). The KTH technology was later licensed and resulted in the first Protein A resin designed for clean-in-place with sodium hydroxide.

Today and tomorrow

Today, Protein A is used in research applications and in the industrial purification of monoclonal antibodies. In the laboratory, Protein A is often used in applications such as immunoprecipitation, sample preparation and drug discovery. At the industrial scale, Protein A chromatography resins are used to purify Fc fusion proteins and monoclonal antibodies that may be used as therapies themselves or as the carrier for a cytotoxin in antibody drug conjugates (ADC). In recent years, protein A has also been used to purify antibody fragments via its natural interaction with the Fab region present on many fragments (13).

Given that Protein A resins are often identified as a relatively large contributor to cost of goods (COGs) in downstream purification, many researchers have attempted to replace the Protein A step with other technologies. Technically feasible alternatives include two phase separations, precipitation, and non-affinity chromatography.However, none of these techniques offer the simplicity, robustness and specificity that Protein A brings to antibody purification. As such, implementation at large scale is extremely limited. Ultimately, Protein A offers better process economy and faster time to market, especially when users develop processes that ensure long resin lifetime (in excess of 100 cycles).

Despite the failed attempts, I have often heard people in the industry discussing whether it will be possible to completely replace Protein A in the future. Given that Protein A has already been well optimized by natural selection and chemical engineering, however, I am not sure if a replacement will ever be necessary.



Best Practices

- Choose a resin with high capacity to ensure that your process can adapt to ever-rising titers in the bioreactor.
- Screen resins at conditions similar to those envisioned at large scale.
- Use high throughput process development (HTPD) techniques to develop post-load wash steps that can reduce host cell proteins (HCP), DNA and aggregates further.
- Always use bioburden reduction filters prior to your Protein A column.
- Use dedicated, low pH "strip" steps prior to clean-in-place.
- Clean-in-place every cycle, with the highest concentration of sodium hydroxide that your process and resin will tolerate.

Since 1978, Protein A productivity and capacity have increased 4.3 and 5.5 percent a year, respectively (14).

That said, there is no need for complacency – and I expect Protein A based affinity chromatography to continue to improve in the future. I expect to see a focus on increased capacity for antibodies and overall reductions in cost of ownership. The cost of affinity chromatography has often been criticized, but, in general, Protein A resins have not become significantly more expensive from generation to generation. In addition, generational improvements in Protein A resins have led to increased productivity of downstream purification (14).

In the future, further improvements in alkali stability will also be important, driven by increased awareness of the risks of bioburden contamination on Protein A columns, which are exposed to high volumes of nutrient-rich cell culture media and subsequently cleaned-in-place with relatively low concentrations of sodium hydroxide. Additionally, there is an opportunity to further increase Protein A lifetime by enabling the use of more concentrated clean-in-place reagents to meet expectations of users (15).

I find the story of Protein A interesting from both a biological and industrial standpoint – and I hope those reading this now have a better appreciation of this everyday protein! Protein A has come a long way since the 1950s, but in reality the narrative is still relatively young. In less than 60 years, science has advanced from discovery in nature to recombinantly-produced, genetically-engineered variants of the protein that are optimized for industrial use. How much optimization will we see in the next 60 years? In an ideal world, the story of Protein A will be repeated for the next generation of therapies that are starting to populate the early clinical pipeline. Affinity solutions would be enabling for adenovirus, cell therapies, virus-like particles and more.

Jonathan Royce is BioProcess Senior Product Manager of Antibody Affinity Resins at GE Healthcare.

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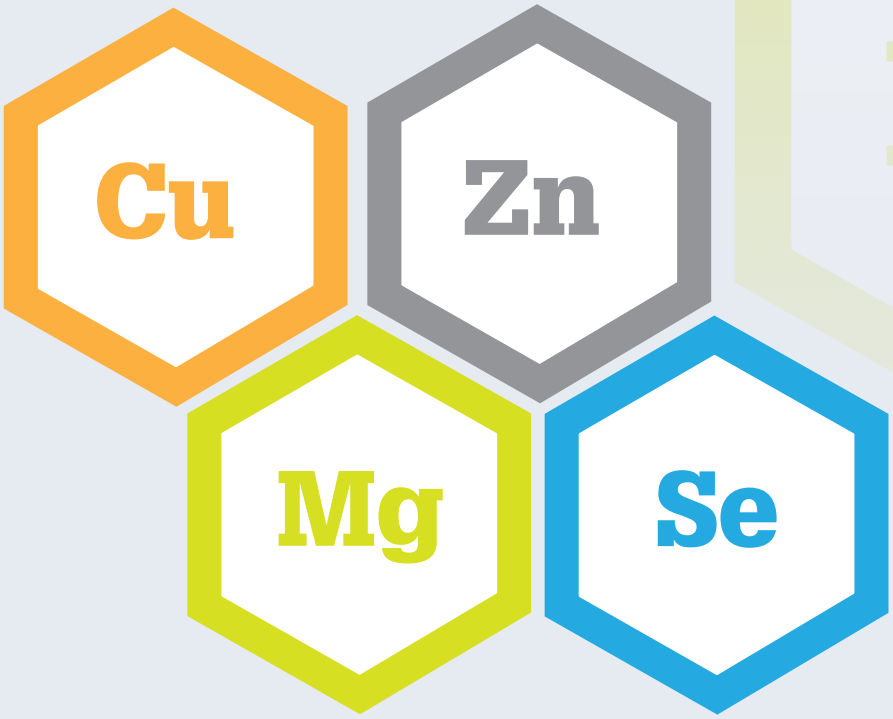

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"We now have a state-of-the-art trace metal analysis facility – the result of significant investment and a real development journey."

Chasing Traces

Variability in raw materials can cause product quality issues and lead to regulatory problems. Increasingly, our industry requires specific reassurance on elemental impurities, so how can media suppliers provide confidence in this difficult area?

By Chandana Sharma

Supply chain integrity and reliability is critical for the biopharma industry, perhaps no more so than in the manufacture of cell culture media. A given medium may comprise of 50 to 80 different raw materials, and low levels of impurities in each component can have a cumulative impact on the final medium composition. Impurities can affect multiple pathways of the cells that are grown in cell culture medium, thus contributing to the variability of proteins harvested from those cells. Some trace metals impact certain glycosyltransferases and can alter the protein glycosylation profile. In particular, concentrations of trace elements like copper, manganese, zinc, and selenium, are absolutely key because they have a direct impact on protein quality. Other trace metals are critical nutrient sources in their own right – iron in particular is essential for cell growth. Whether the trace metal is intentional in the media formulation or an impurity, trace components have different effects and "ideal" concentrations may vary according to the process in question. To avoid product quality issues, it is vital that biopharma and biosimilars companies understand the effect of elemental metals on a given bioprocess, and quantify the impurities present in their processes.

Regulatory goals

Recognition of the critical impact of trace metals is reflected in evolving regulatory guidelines. The pharma industry is currently adjusting to new guidelines, such as the FDA's ICH-Q3D "Elemental Impurities" document, concerning acceptable impurity levels in drug products. Broadly, regulators now favor replacement of traditional analytical chemistry methods with more sensitive techniques for trace metal quantification, such as inductively-coupled plasma mass spectrometry (ICP-MS). Industry must familiarize itself with these methods – and media suppliers must adapt to this trend. So how is Merck KGaA positioned in this environment?

We now have a state-of-the-art trace metal analysis facility – the result of significant investment and a real development journey. When we first started fully characterizing raw materials, we didn't initially think about trace metals; however, on closer inspection, we saw surprising variability in elemental impurities and realized that we needed to expand our dataset to make sure we understood our raw materials relative to trace metal impurities. As we collected more data, it became increasingly clear that the issue needed serious attention. Unfortunately, the external analytical laboratory that we used at the time wasn't providing us with the data we needed – they worked at a parts per million sensitivity when we needed parts per billion. Eventually, we made the decision to develop an in-house, dedicated facility for the analysis of

elemental impurities. We renovated our existing space, procured a high quality ICP-MS instrument, hired some personnel, and started generating our own data. We chose ICP-MS as the workhorse analysis method because it is about as exact and quantitative as you can get, but we do sometimes also use ICP-AES (atomic emission spectroscopy) or ICP-OES (optical emission spectroscopy), depending on the quantity of the element we are studying. In general, however, we rely heavily on ICP-MS.

In short, we quickly went from not even knowing that we should look at trace metals to a purpose-built, in-house facility dedicated to the analysis of elemental impurities.

Measuring what's there – and what it does

Our elemental impurities initiative is a three-tiered approach: i) quantifying trace metals in individual raw materials and in our final product; ii) determining whether our process of mixing and milling these raw materials itself contributes to impurities in the final product; and iii) understanding the impact of individual impurities on final protein quality. The first element was perhaps the most time-consuming, but the third part – understanding impact on protein quality – was the most important. To study this, we also utilize a CHO model system that produces a specific protein where we can assess the impact of elemental impurities on the ability and quality of the protein. The findings will not apply to all biopharma processes, but given that 70 percent of the biopharma industry uses CHO cells, the data is relevant to most systems.

One example of impurities I'd like to share is our learnings around ferrous sulphate. Cell culture formulations and cells in general, must have a source of iron. Ferrous sulphate is a common choice. Ferrous sulphate is sourced from mining from the earth and as such may have companion ingredients in the form of impurities. We found that our ferrous sulphate had very high levels of manganese, which in parallel the industry was learning had a high impact on protein quality. We changed our ferrous sulphate supplier to one that offered a product with a lower manganese level. To our surprise, however, one of our clients then reported a sudden change in the glycosylation profile of their product. Our subsequent investigations showed that this was caused by lower manganese levels in the medium, which was a consequence of our switch to a more pure ferrous sulphate. Essentially, the client's process relied on manganese impurities for the required product profile. It was easy to fix with a manganese supplement, but the case serves as an interesting example of how a higher quality product can have an unexpected negative impact. (I might add that, for most customers, reducing the manganese impurity level was a positive development!) The whole topic really emphasizes the importance of understanding a product and its processes; it is unwise to rely on impurities for a bioprocess; far better to understand what the process requirements are, and then work with media suppliers to ensure those needs are met.

Another example of the importance of being able to accurately track down and quantify trace metal contamination also involved manganese. We were working with a customer to establish the source of a ten-fold excess of manganese in certain lots of the same cell culture medium. After many dead ends, we isolated the source of the manganese in the most surprising culture component: vitamins. Vitamins are synthesized using processes in which impurities are well-controlled, so this was unexpected. Nevertheless, a specific lot of vitamin B6 had up to 500 ppm of manganese, and was clearly the source of manganese contamination in the final product. Once again, we fixed the issue by working with our vitamin B6 supplier, and again it shows how a sophisticated trace metal analysis initiative can help identify even the most unusual problems.

Control and customization

At Merck KGaA, our growing understanding of the effects of elemental impurities, and the expertise we have developed in the quantitative analysis of trace metals, has led us to focus on our raw materials and ensure that each individual material is as pure as possible. By ensuring that each component is high quality, we minimize the cumulative effect of impurities on the final culture medium and, hence, on protein quality. From the data we collect through our three-tiered approach, we continually modify our systems and guide ourselves to do things better, and to make better supply chain decisions.

Looking ahead, we have identified a market need for a customized trace metal analysis service. We are now in the process of developing this as a formal offer to help clients quantify trace metal impurities in their cell culture media. It also matches our philosophy of data visibility. Making data available to customers allows them to manage process variability according to their needs; for example, by mixing different batches of medium to ensure the cells receive optimal levels of given trace metals. Raw materials will never be 100 percent clean, but if you can measure impurity levels, you can manage impurity levels. Without a data-driven approach, it is far more difficult to control the impact of trace metal variability on bioprocesses.

My advice for industry is this: first, understand your particular process; second, communicate with your media supplier to ensure you build robustness into your supply chain; and third, use data to design a process that achieves the desired product profile.

Chandana Sharma, PhD, is Head of Cell Culture Raw Materials, Upstream R&D, at Merck KGaA.

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Plant Power

How much untapped potential do plants have for both discovering and manufacturing drugs?

In the June issue of The Medicine Maker, we delved into the potential power of the cannabis plant and why it could lead to new medicines for unmet needs (http://tmm.txp.to/0617/cannabis). However, cannabis is not the only plant that could have practical uses in the pharma industry. When it comes to drug discovery, Cassandra Quave urges the industry not to overlook ethnobotany, particularly when it comes to the search for new antibiotics, while Johannes F. Buyel believes that plants, such as tobacco, could have a role to play in manufacturing.

Green Fingers

By Cassandra Quave

Even in early childhood, I was always interested in medicine and plants, and I have fond memories of my mother teaching us how to slice open the aloe plant in our backyard and apply it to treat burns. My earliest scientific interests ranged from microbiology to emergency medicine, but in college I became fascinated with anthropology and ecology – and this ultimately culminated in two research trips to the Peruvian Amazon during my senior year. Those trips to the Amazon, where I worked with a shaman and learned about the important role of botanical medicines in the ethnopharmacy of the region, solidified my path towards this field. Today, I run the Quave Research Group at Emory University in Atlanta, USA, which is composed of an interdisciplinary team of scientists passionate about translational science geared towards the improvement of human health. Our research group takes the ethnobotanical approach (the study of human interactions with plants) to drug discovery, and one of our focuses has been to try to discover new solutions for one of the world's most pressing medical issues: antibiotic resistance. Our research has already shown that some medicinal plants are good sources of novel compounds that can be developed and used to either enhance or restore the efficacy of existing lines of antibiotics.

Plants are a great place to look for new medicinal compounds because they produce a broad array of biologically active compounds used in their defense, as well as to attract pollinators and seed dispersers to compete with other organisms in their biological niche. Before the golden era of antibiotics (1950s), plant products represented more than one fifth (22 percent) of all new chemical entities used in medicine. Plant life can provide a rich source of medicinal compounds, as only a very small fraction of the known plant species on earth (the total estimated at ~450,000) have been investigated for the presence of antimicrobial compounds – and only 1 to 10 percent of this total number are currently exploited by humans for medicine. Over the years, we have worked with many fascinating plant species. Today, we have extracts for more than 400 species in the freezer and in the line-up for various bioactivity screens. If I had to pick the top three most fascinating species we've worked on so far, it would be Castanea sativa (sweet chestnut), Rubus ulmifolius (elmleaf blackberry) and Schinus terebinthifolia (Brazilian peppertree). Each is used in traditional medicine for the treatment of skin infections, and yet none inhibit bacterial growth. Instead, we discovered that each interferes with other processes important to infection (biofilms and virulence factor production).

We have only begun to scratch the surface in the scientific exploration of the pharmacological potential of plant natural products. Despite their frequent use in various traditional medical systems and as dietary supplements, we still have much to learn concerning the safety and efficacy of the majority of plant ingredients in use. Based on our findings concerning medicinal plants used for the treatment of infectious disease, I think that they may be among the most underappreciated plants based on the ways in which they have been tested in the past. The most common models used to assess the antibacterial impact of plant extracts and isolated natural products has been for growth inhibition, but we need to move beyond this simplistic view and ask additional questions around how else they might work on the pathogen or the host.

Two of our major projects right now focus on isolation and de novo structure identification of novel natural product inhibitors of Staphylococcus aureus

"Plants are a great place to look for new medicinal compounds because they produce a broad array of biologically active compounds used in their defense."

communication (quorum sensing inhibitors). We plan to investigate how these compounds, which shut down communications and virulence factor production, can be used to treat different types of staphylococcal infections in the future. We are also screening the Quave Natural Products Library (composed of more than 1,000 extracts from over 400 species) against high priority multidrug resistant pathogens, including superbugs like carbapenem resistant Enterobacteriaceae and multidrug resistant fungi, such as Candida auris. We are looking not only for new chemical entities that can target the growth and survival of these pathogens, but also compounds that can restore or enhance the activity of existing lines of antibiotics and antifungals, or act via completely novel pathways.

The problem with working in this field – as for many others in science – is science funding. We have some really exciting leads on our hands, but it is always difficult to convince traditional funding gatekeepers to support our work on natural product mixtures. The current drug development paradigm is extremely focused on single target, single compound approaches, whereas many natural products work better when tested in mixtures. This presents an inherent problem with achieving fundable scores in grant review sessions. We also need a more open mindset concerning mechanisms of action of future anti-infectives. We need to invest more funds, time and research resources towards exploration of non-traditional anti-infective pathways, such as virulence inhibitors, biofilm inhibitors, antibiotic sensitizers, and even host-targeted therapies. I'd love to see the pharma community pay more attention to plants and other natural sources of new compounds.

Cassandra Quave is the Curator of the Emory University Herbarium and Assistant Professor of Dermatology and Human Health, Atlanta, GA, USA.

Plants: the New Medicine Makers

By Johannes F. Buyel

Biopharmaceutical proteins are one of the central pillars of modern healthcare systems. The simplest polypeptides can be produced in bacteria or yeast, but more complex proteins and glycoproteins are produced in mammalian cells – the current gold standard among biomanufacturing platforms. But plants, particularly tobacco due to its biomass yield, are receiving increased attention for the niche product market. Potentially, plants could present greater economy, scalability and sustainability for mainstream biopharma manufacturing. But in the face of strong incumbent technology and intense competition, can these relative newcomers stand their ground?

Biopharmaceuticals include vaccines and prophylactic antibodies for disease prevention, labeled antibodies and ligands for disease diagnosis/monitoring, and diverse therapeutic proteins ranging from replacement enzymes and hormones, to antibodies that target and destroy cancer cells. Some of these proteins, such as insulin, serve large markets, but the vast majority, including most antibodies, are indicated for diseases with a relatively low incidence. In these cases, the entire annual global demand is typically in the kilograms to hundreds of kilograms range. A few antibodies have achieved blockbuster status and the demand for these exceptional products is several tonnes per year, but if we want to use antibodies for the prevention, diagnosis or treatment of more widespread illnesses, including Alzheimer's disease, malaria or HIV/AIDS, then demand may increase to 100 tonnes per year or more for each product. Meeting such demand will be difficult using microbes or mammalian cells because the scalability of a production suite is limited by the working volume of today's largest bioreactors, typically 20,000 L for conventional stainless-steel fermenters and 2000 L for single-use alternatives. Assuming optimal yields, constant campaigns and consistent perfect performance, such facilities would produce 7.5 and 0.75 tonnes per year, respectively (1).

"Plants could present greater economy, scalability and sustainability for mainstream biopharma manufacturing."

The obvious solution to match supply and demand is to commission parallel systems with multiple bioreactors operating simultaneously, or to build additional production facilities. The problem with this approach, however, is the cost of the infrastructure. Monoclonal antibodies are among the most expensive drugs currently available on the market, in part due to the high cost of manufacturing. Costs are borne by patients and healthcare providers because the target population for these drugs is relatively small, and the treatment course relatively short. Antibodies developed to prevent the transmission of prevalent diseases, such as HIV/AIDS would need to be administered as a long term regular microbicide to tens of millions of at-risk people, most of whom live in countries with sparse healthcare resources. The costs need to come down. And to achieve this, the industry needs a new manufacturing paradigm. It's well worth considering plants.

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"Individual plants can be viewed as living, single-use bioreactors that can be grown from seeds."

The green advantage

The use of plants for the manufacture of biopharmaceuticals was first demonstrated in 1989 but, for a long time, the industry viewed this as a fringe movement because of the untested nature of the technology, low product yields, and absence of a regulatory framework. In comparison, mammalian cells are reliable, yields regularly exceed 5 g L^{-1}, and the regulatory framework is rock solid. Over the last few years, however, plants have started to flourish, (both metaphorically and literally) as a new production platform. Expression levels of ~3 g kg^{-1} biomass have been achieved (2). Together with the infrastructure available from industrial agriculture, we could "farm" antibodies and other biopharmaceutical proteins at unprecedented scales; the cost of growing more plants is tiny compared with the costs of building more fermentation suites (3).

Individual plants can be viewed as living, single-use bioreactors that can be grown from seeds, using virtually free and unlimited resources (sunlight and water). Plants have no compatibility issues with other equipment, and the costs for cleaning and disposal are minimal (composting, compared with thermal deactivation of fermenter waste). Plants also do not support the propagation of human pathogens and have a built-in barrier to prevent contamination with mammalian viruses (3). Genetically modified plants are primed with the means to produce the biopharmaceutical product, analogous to a transformed mammalian cell line. As an alternative, unmodified plants can be used for transient expression by infiltrating the leaves with appropriate vectors. The advantage of transient expression is that production can be ramped up quickly – indeed, much more quickly than any cell-based process (4).

Safety and scalability aside, plants also offer several advantages over mammalian cells in terms of product specifications. For example, plants can produce glycoproteins with diverse glycan structures, allowing for the development of products with designer quality and functionality profiles, such as extended serum half-life, preferable interactions with immune system cells, and modified antibody effector functions (5). Plants can also produce proteins that are highly toxic towards mammalian cells, such as antibody–drug conjugates, which are currently produced in a complex process involving mammalian cells for the antibody component, and microbes for the toxin, followed by in vitro conjugation and further purification. All of this could be achieved in a single plant, with only one round of downstream processing and purification. One major difference between mammalian cells and plants is that the former secrete products into the medium, whereas proteins expressed in plants, such as tobacco, must be released by shredding and grinding the leaves. Although this requires extra clarification steps to remove the resulting particulates, the process flows are similar for plants and mammalian cells and there is now little difference in costs – an important consideration given that downstream processing can account for up to 80 percent of all production costs (3).

I believe that the advantages of plants in terms of safety, scalability, sustainability and product diversity can be valuable economic and environmental assets when competing with mammalian cell cultures, even though the latter are well-established and trusted by industry. The best way to overcome industry inertia and embrace disruptive technologies is to focus on the cost-effective production of relevant biopharmaceutical proteins – niche products that benefit specifically from the advantages of plant-based systems. Plants already stand their ground in these niche markets, but it is likely they will begin to encroach on the markets for more mainstream biopharmaceutical proteins as the technology takes hold.

Johannes F. Buyel is head of the Integrated Production Platforms department at the Fraunhofer Institute for Molecular Biology and Applied Ecology IME, and senior scientist at RWTH Aachen University, Germany.

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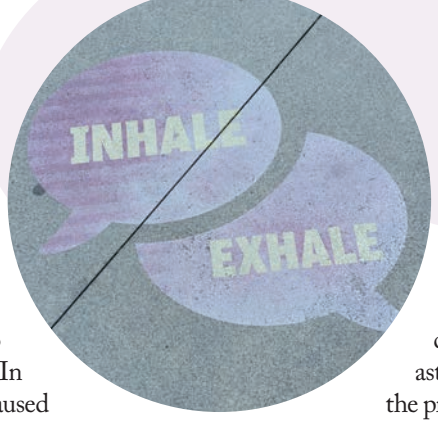

Raising Respiratory Awareness

Respiratory drug development lags behind other therapeutic areas, but why? And what new advances could help shape the future?

By Robert Lins

Great strides have been made in medicine as of late, with the recent approval of Kymriah – the first CAR-T therapy – being heralded as a breakthrough. Certainly, the cancer field is seeing a number of exciting drug development projects, but other fields are being left behind. The field of respiratory medicine, in particular, is plagued by unmet needs. First of all, there is very little awareness of respiratory disease at all. For chronic obstructive pulmonary disease (COPD), for instance, diagnosis rates can be as low as 30 percent (1,2) resulting in unnecessary delays in treatment initiation. Even when a patient is correctly diagnosed, treatment is often less than ideal. Moreover, there are clearly unmet needs in the treatment of COPD, such as exacerbation and symptom control, improving health status, and slowing the decline of lung function and disease progression (3). Although there is considerable evidence that bronchodilators provide lung function improvements, as well as clinical benefits in patients with COPD, inhalable drugs often cause compliance issues due to the difficulty of correctly administering pulmonary or nasal formulations – research has estimated that only 1 out of 10 patients with a metered dose inhaler performs all of the steps correctly (4).

Patients with respiratory diseases need new medicines that alleviate symptoms and modify the course of the disease without, at the same time, causing undue side effects and/or non-adherence to medication regimens. In 2015, COPD alone caused 3 million deaths – accounting for 5 percent of all deaths globally (5) – but despite this there are few treatments being investigated in industry pipelines. Many other respiratory conditions are also being neglected, including orphan diseases such as cystic fibrosis, idiopathic pulmonary fibrosis (IPF) and pulmonary arterial hypertension (PAH). Non-inhaled drugs, particularly oral or sublingual formulations, are expected to be particularly welcome from a compliance perspective.

Rising to the challenges

Many believe that respiratory medicine is a stagnating field (6), which is unacceptable given that the incidence of respiratory disease is rising with air pollution and reduced birth rates (the elderly are far more prone to respiratory disease). Researchers and the industry have significant work to do, but the question is where do we start?

Rising costs of drug development affect all therapeutic areas, but in respiratory medicine the economic difficulties are exacerbated by high attrition rates and chronic underfunding. Respiratory drug development is difficult and the lack of available treatments can perhaps be partly attributed to a shortage of critical tools in the areas of biomarkers and clinical outcome measures. Hence, advances in precision medicine and targeted treatments seen in fields such as oncology simply have not been reflected in the respiratory field. Notably, in terms of measuring patient-relevant outcomes in respiratory drug trials, investigators currently rely on classical, subjective evaluation methods; in particular, forced expiratory volume over one second (FEV1) and forced vital capacity (FVC). These outcome measures remain standard, yet often show poor correlation with patient-relevant outcomes, such as quality of life and mortality – and therefore are of limited use. When managing chronic diseases such as asthma, tools that permit the prediction of functional decline are essential – methods that merely plot deterioration over time can only get you so far.

So where might new tools come from? This question points to another problem: the paucity of molecular targets to guide the development of respiratory biomarkers and drugs. Oncology is rich in targets that suggest new drug-biomarker possibilities. A shortage of biomarkers in respiratory medicine – including both laboratory tools and clinically validated biomarkers recognized by regulatory authorities – makes monitoring and assessing patients difficult. And without a biomarker to use as a surrogate endpoint, clinical studies are rendered far more difficult, so it's no wonder there is a lack of advanced drugs in the respiratory field. Regulatory requirements are notoriously strict and many of today's tools just do not offer the required accuracy.

That said, there have been some promising – albeit small – success stories in recent years. At the level of basic research, there have been advances in the understanding of the aetiological role of cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations. This knowledge has been translated into two marketed products: Vertex's Kalydeco (ivacaftor) – the early development of which was funded by the Cystic Fibrosis Foundation – and the combination product Orkambi (lumacaftor/ivacaftor). These are now helping at least the small proportion of patients who have the CFTR mutation targeted by these drugs. Cost, however, is an issue; in the UK, for instance, Orkambi is considered too expensive by the country's cost watchdog NICE (The National Institute for Health and Care Excellence). Additional drugs currently in pipelines will, hopefully, address other CTFR mutant genotypes in the future.

On a clinical level, developments in monoclonal antibody therapeutics are

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particularly promising, notably for treating inflammatory diseases by targeting immunoglobulin E and cytokines such as interleukins (IL) 4, 5 and 13. One example is the IL-5 targeting antibody Nucala (mepolizumab) from GlaxoSmithKline, which is licensed to treat severe asthma. Investigative products in this field include Medimmune's IL-5 antibody benralizumab, and Regeneron's IL4/13 antibody depilumab – these treatments have shown real promise and could signal a positive shift in the treatment of COPD and asthma. Similarly, in the field of anti-fibrotics for IPF, encouraging progress is evident: Boehringer Ingelheim's Ofev (nintedanib), and Intermune's Esbriet (pirfenidone) recently reached the market, and the IPF development pipeline includes some very exciting drugs, not least stem cell therapies. Finally, of course, lung cancer therapies move apace, both with regard to recent approvals and to drugs in the pipeline.

Changing times

These advances are a good start to a new tide of innovation in respiratory development, but progress would be significantly faster if researchers and industry had access to advanced biomarkers and better methods of measuring and predicting outcomes. That said, some changes are evident in the field: for example, measurement of fractional exhaled nitric oxide (FeNO) is increasingly used as an outcome in respiratory clinical trials, as it is considered to be an easy way to measure inflammation. Also, plasma fibrinogen was recently (September 2016) accepted by the FDA as a biomarker for studies examining exacerbations in COPD; however, it has not been broadly taken up in the clinician community. In the research arena, eosinophil levels in sputum and blood are commonly used as a marker and also as a selection criterion; initially, this method was mainly used to measure outcomes after treatment with inhaled corticosteroids, but it is now often used to assess the effect of anti-inflammatory monoclonal antibodies. Similarly, interleukins, such as IL6, may hold promise as outcome parameters in inflammatory disease; as yet, however, these have not been formally validated, let alone recognized by regulatory authorities. At an earlier stage still, periostin, which binds to certain integrins, is showing promise as an inflammation indicator inTH2-mediated asthma. Similarly, copeptin – which is the C-terminal fragment of provasopressin, and thus a surrogate marker for vasopressin – has potential as a biomarker for cardiovascular risk. Since cardiovascular risk is increased in COPD and other inflammatory diseases, elevated copeptin levels may be relevant in the respiratory field.

There is also more reason for optimism in the field of outcomes measurement in respiratory medicine. Forced oscillation technique (FOT) is a new method that is increasingly used in clinical trials of respiratory therapies. This non-invasive technique measures the mechanical properties of the respiratory system across a wide range of frequencies. In addition, unlike spirometric techniques, it does not require active patient participation. Another advantage of FOT is that it makes measurements at the small airway level, which enables it to provide a better picture of disease progression than methods that rely on measurements from the large airways. Quantified imaging techniques also hold great promise, although none have yet been approved by regulators. One such technique is functional respiratory imaging, which creates 3D segmented computer models of the lungs using techniques such as computed tomography, magnetic resonance imaging and ultrasound. Subjecting these models to analytical methodologies derived from the aerospace industry – in particular, computational fluid dynamics and finite element analysis – provides invaluable information on pulmonary function and post-inhalation distribution of drug particles.

On the data side, the introduction of electronic clinical outcome assessments (ECOAs) is also having an impact on respiratory drug development. In ECOA, outcomes data from electronic patient records are integrated with lung function measurements, using a single device; these data are linked to a server by a safe internet connection, thus enabling data to be collected at the patient's home and made immediately available for analysis. While not unique to the respiratory area, this innovation could have a significant impact by demonstrating whether a drug is providing sufficient benefit.

An improved understanding of inflammatory mechanisms is likely to lead to identification of respiratory disease-specific targets, which in turn could lead to the investigation of new treatment modalities, hopefully within the next four or five years. Genetic therapies, too, may finally live up to their initial promise – albeit in the slightly longer term – particularly in cystic fibrosis and pulmonary arterial hypertension. In the near term, however, there is hope that -omics analysis will lead to new diagnostic tools, biomarkers and outcome measures. With luck, these could offer real benefits to respiratory disease patients in the coming years – and lead to a new boom in respiratory drug development.

Robert Lins is SGS's Clinical Research, Respiratory Project Director.

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Renaissance Man

Sitting Down With... Cornell Stamoran,
Vice President of Corporate Strategy,
Catalent Pharma Solutions, USA.

Did you always want to work in pharma?

The short answer is no! My undergraduate degree was actually in accounting, and after graduation I went to Arthur Andersen, where I worked as a Certified Public Accountant serving mostly hospital and financial clients. After five years working for the firm, I wanted a change – with less travel – so I reached out to a friend and former colleague for advice. He had moved to R.P. Scherer Corporation, which was then the leading global drug delivery technology provider. He said there was a role open, for which he believed I was uniquely qualified. So I applied, and 25 years ago in September I joined the company – and the pharma industry, beginning a journey of continuous learning.

How have your roles within the company changed over the years?

Early on, I focused on financial reporting, which meant I had to learn the business in depth, from learning the market to competitive delivery technologies. This became even more important as I moved into financial strategy and supporting M&A. Then in 1998, when Cardinal Health bought R.P. Scherer, I had to make a decision: go back into accounting, or continue down the "top line" trajectory focused on strategy, offerings, customers and markets. I chose the latter, and haven't looked back since.

Things then took a slightly different turn when Cardinal Health created the predecessor of Catalent in 2000; I was asked to put together the new company's customer story and build the brand – something I hadn't done before. I was fortunate enough to bring someone in who knew the technical side of marketing inside-out, which meant I could continue to focus on strategy.

Over the years, I've been involved in advocacy for the company's interests with diverse audiences, including investors, customers, media and, most recently, regulators and legislators. I've also engaged in advocacy via industry groups and I have served on advisory boards for several long-standing industry conferences and publications. More recently, I joined the Finance Committee of the Controlled Release Society (CRS), and also serve as a trustee of the CDMO trade association, Pharma & Biopharma Outsourcing Association (PBOA). Along with other co-founders, I also helped establish the Catalent Applied Drug Delivery Institute to advocate for more effective use of formulation and drug delivery to produce better patient outcomes.

How important is recognition for CDMOs?

I think it's important for everyone participating in the pharma and biotech industry to have some understanding of the critical role that outsourcing providers play in the pharma industry today – by our estimate, for example, one in 20 doses is made by Catalent, and around 1 in 6 by CDMOs generally, so we need CDMO-focused advocacy in Washington and Silver Spring. With debates over drug pricing in the US and elsewhere, an ill-advised regulatory measure could affect companies like ourselves, who aren't involved in drug pricing to the end market.

It's also important to appreciate the role outsourcing has played in increasing the competitiveness of the pharma industry. The maturing CDMO sector, along with a shift towards specialty drugs, has given smaller companies the option to take their development programs to market themselves, in a way that was rarely possible in the early part of my career.

How do you approach advocacy with the FDA?

One recent example of unintended legislative impact on CDMOs was the Generic Drug User Fee Amendments of 2012 (GDUFA 1) in the US. CDMOs didn't have a seat at the industry table when the agreement was first negotiated, and we believe that it imposed an economically disproportionate share of the burden to CDMOs. This was one of the primary factors in CDMOs forming a trade association, and one of our early accomplishments was to gain a seat at the table on the industry negotiating team for the reauthorization of GDUFA. As a result of that long-duration engagement with the FDA, we've started to build a stronger and deeper understanding of the place of CDMOs in the industry, and the contributions we can make to the regulatory policy process.

Tell us about your work in patient adherence...

During part of my tenure, I was fortunate to work closely with both healthcare packagers and public health experts, and came to understand the critical role that patient adherence plays in ensuring treatment outcomes. With that knowledge, I began to look at drug delivery very differently, and realized that many new drugs had product design features that could potentially negatively impact patient outcomes.

After conducting a physician survey to understand why patients stop taking their drugs, we learned that drug product design can have a direct impact on patient outcomes – sometimes in surprising ways. For example, we found that the color of the tablet or pill matters. We also identified that more than half of the drugs approved since 2009 had some design characteristic that, if addressed, could likely generate better patient outcomes.

Another thing we found was that people at the front lines of product development rarely have sufficient information about the patient journey to inform their drug product design choices. Only one in four development scientists surveyed said they took into consideration real world research on drivers of patient treatment adherence/discontinuation when making product design decisions. We're passionate about filling that gap by bringing such research to the industry.

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