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Online this Month

Making European Regulations Work

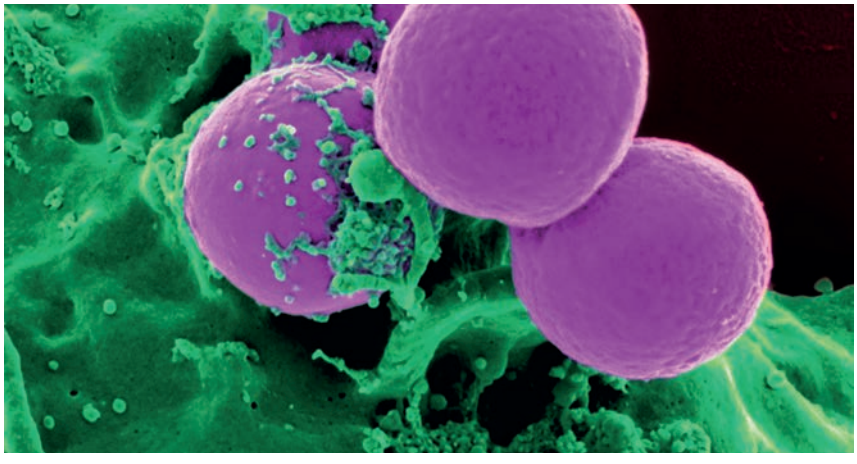
A report released by Escher's TI Pharma platform claims that the European regulatory system for medicines can be used in a more "efficient and effective manner." At a first glance it may seem as if the report is damning the system but that certainly isn't the case. Read our summary online to find out what issues were identified.

Read it online: tas.txp.to/0314/euroregs

A New Approach to MRSA

We report on the first endolysin registered for human use against methicillin-resistant Staphylococcus aureus (MRSA) on page 12. Online, we bring you an interview with a clinical microbiologist, Bjorn Herpers, so that you can find out more about phage endolysins and why some people believe that they are a promising new strategy in the fight against drug-resistant bacteria.

Read it online: tas.txp.to/0314/mrsa



Supercomputers to the Rescue

On page 35, Catherine Akers examines the challenges of adverse drug events for biologic medicines. On our website you can read about the efforts of researchers to tackle side effects much earlier in the drug development process. Looking for ways to 'red flag' candidate drugs for serious side effects, a team from Lawrence Livermore National Laboratory has used supercomputers to link proteins to side effects.

Read it online: tas.txp.to/0314/supercomp

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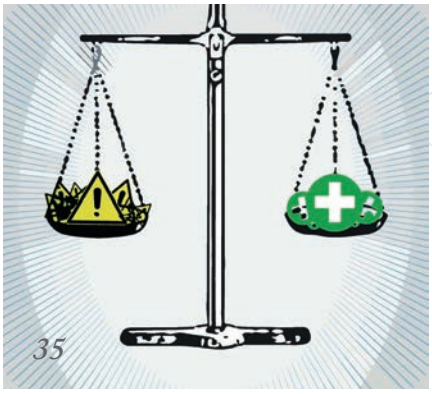

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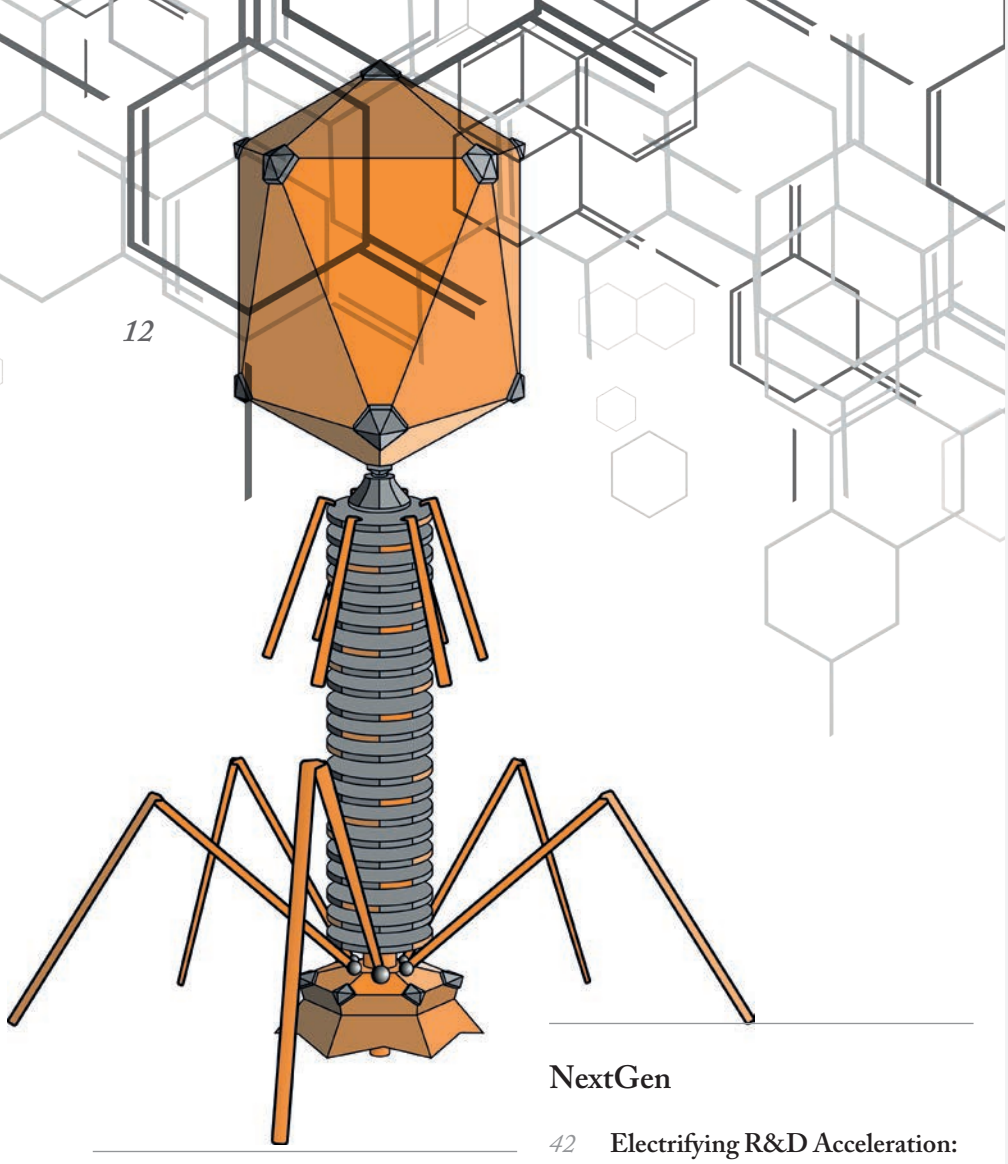

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the Medicine Maker

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Big Bad Pharma?

The Ebola media frenzy has reminded the public how selfish our industry is. But, somehow, that doesn't sound quite right...

The ongoing Ebola outbreak seems to have highlighted the pharmaceutical industry's continuing reputation problem. While some commentators have praised drug makers' swift response (1), others have blamed companies for not developing a vaccine earlier, accusing them of putting profits ahead of patients (2).

Public opinion still puts pharma well below technology, retail and energy sectors (3), and the only healthcare field less trusted by patient advocacy groups are for-profit health insurers (4). Why are pharma companies – who manufacture life-saving drugs – so unpopular?

Certainly, a number of high-profile scandals, involving corruption, cover-ups and dodgy deals, have seriously damaged the industry's reputation. But perhaps the most pervasive criticism arises from the tension between profits and people, business and society. Specifically, in the case of Ebola, newspaper columnists, academics and even the WHO have attacked the pharmaceutical industry for failing to devote sufficient resources to finding a vaccine.

However, for defenders of the industry, these accusations seem wide of the mark. Firstly, pharma companies *have* been conducting work in this area – both Johnson & Johnson and GlaxoSmithKline have vaccines under development, for example. Secondly, while Ebola is unquestionably a terrible disease, until now outbreaks have been small, affecting at most a few hundred people. Until this year, fewer people were dying of Ebola than seasonal flu. Meanwhile, diseases such as malaria, HIV/AIDs and TB kill millions every year. Even if pharma didn't have to consider profits, is it really surprising that only a few companies have chosen to focus on Ebola?

I believe the majority of pharma industry employees are very aware of its special role in society. Medicines are not simply products – and the companies that make them expect to be held to a higher standard because of that. No-one is trying to claim perfection. Companies walk a fine line between their duty to shareholders and their duty to society as a whole; it's no revelation that the tireless pursuit of profit can lead to shocking acts of greed and corruption.

But it's important not to lose sight of what the industry has achieved. Breakthroughs made by industry scientists have helped to revolutionize modern medicine, and you only have to look at the latest Access to Medicines Index (page 11) to see that big pharma companies are doing more every year to improve healthcare in the developing world.

The senior executives and researchers I speak with all have something in common: they are proud of the part they have played in moving medicine forward – they are proud to be medicine makers – and we are proud to celebrate their achievements.

Charlotte Barker
Editor

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Catherine Akers

Currently Regulatory Affairs Manager at Amgen, UK, Catherine Akers began her career as a clinical research associate, monitoring the conduct of clinical trials and visiting doctors responsible for trialling new drugs. "The collection of safety events for subjects is key in any clinical trial but that is only the tip of the iceberg," says Catherine. "The continued collection of safety information once a medicine is in use ensures that benefits and risks can be carefully assessed throughout a product's lifecycle." As the safety of drugs continues to make newspaper headlines, Catherine believes that more measures to monitor the safety of medicines can only be a good thing. And that is where she is today; using her knowledge of drug development and current legislation to advocate for increasingly robust practices for the collection of safety events.

Catherine talks us through the challenges of pharmacovigilance for biologics on page 35.

Steve Thomas

Graduating from Warwick with a chemistry degree, Steve Thomas joined the nuclear magnetic resonance spectroscopy (NMR) department of Merck's Neuroscience Research Centre at Terlings Park in 1990. "The wealth of experience in medicinal chemistry support made me analytically bilingual; speaking both NMR and mass spectroscopy." Closure of the site in 2006 led him to the Biotransformation and Drug Disposition group at GlaxoSmithKline. "I have always loved puzzles and science," Steve explains, "and structural identification is a straight combination of the two". Having studied metabolic transformations his entire career, eventually, the lure of more challenging samples and close proximity to the development compounds that change people's quality of life proved too strong.

Steve urges us to share data and knowledge on page 18.

Ayman Chit

"Through my career I have always followed my passion and backed it up with as much rigor and discipline as I could. This is all paying off now nicely as I feel intellectually challenged and satisfied doing my bit to propel public health forward." Ayman Chit is currently head of Health Economics, Modeling and Market Access at Sanofi Pasteur in North America. He started off with an undergraduate degree in chemistry and then moved on to study under the Master of Biotechnology program, both at the University of Toronto. Ayman says, "The Masters program was jointly run by the the Business School and the Faculty of Science and it helped me discover that my real calling was in economics. I then quickly moved on to completing a PhD in Health Economics, specializing in the economics of pharmaceutical development and valuation."

Ayman demystifies the economics of drug development on page 17.

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Upfront

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

We welcome information on any developments in the industry that have really caught your eye, in a good or bad way.

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The Final Frontier?

The Galactic Grant Competition encourages companies to use the International Space Station for pharmaceutical R&D

We're used to hearing about national or regional attempts to bolster innovation, but how often do we see an initiative offering companies the chance to conduct research in space? And while we certainly aspired to pharmaceutical development and manufacturing on Mars in our very first cover feature in September, it was admittedly somewhat tongue-in-cheek...

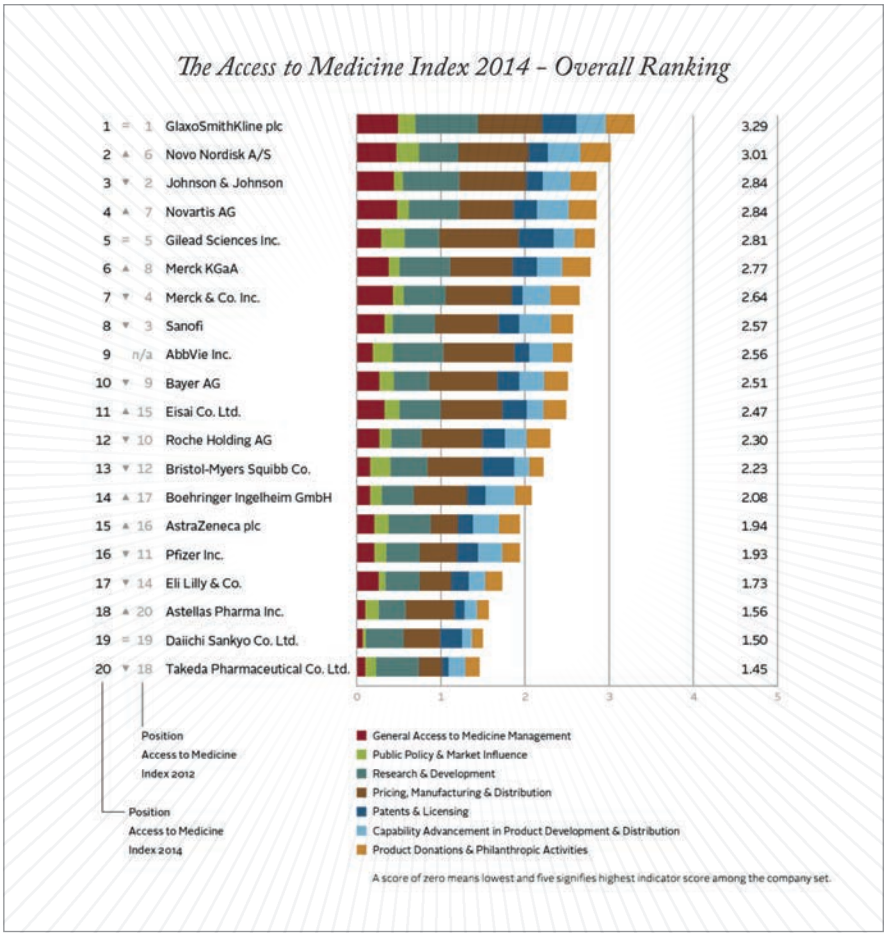
Enter the boldly titled 'Galactic Grant Competition' – an initiative that stems from a partnership between the Center for the Advancement of Science in Space (CASIS) and the Massachusetts Life Sciences Center (MLSC). Sadly, only open to companies based in Massachusetts, the competition presents the opportunity to use the International Space Station (ISS) for research. According to CASIS, the microgravity environment on board the space station has "profound and unique effects on biological phenomena and can enable discoveries with terrestrial applications, including drug discovery, development, delivery and diagnostics."

A number of pharma-related projects are already underway on the ISS. For example, Novartis sent mice to the station to study muscle atrophy caused by extended microgravity exposure from spaceflight, and the Veterans Affairs Medical Center is using a yeast-based system to study cancer drug mechanisms and side effects at the cellular level; the unique environment causes changes in the yeast's metabolism compared with earth-based investigations.

Applications opened on December 1, 2014, and will run until April 3, 2015, and the winners will be announced on July 7, 2015, as part of the ISS Research & Development Conference. *SS*

Access All Areas

The 2014 Access to Medicine index shows progress – but companies remain "conservative"



Are pharma companies doing enough to improve access to medicine in developing countries? It's a question that is very much in the public eye right now, given the Ebola crisis. According to the 2014 Access to Medicine Index, released in mid-November, companies are getting better at facilitating access, but there is still some way to go.

Wim Leereveld, founder and CEO of the Index, featured in our first "Sitting Down With" interview and explained its ambitious aims (see tas.txp.to/0114/wim). In a nutshell, the Index is released every two years and ranks leading pharma companies on their efforts to improve access to medicines in developing nations. You can see the top performers in the table, and how their rankings compare with last year.

Starting with the positive, the Index shows that the number of "relevant" products in the pipeline has grown; for example, Merck & Co. is investigating a new antifungal drug for the neglected tropical disease Chagas, and GlaxoSmithKline is developing a low-cost inhaler and chronic obstructive pulmonary disease drugs for use in developing countries. Since 2012, several important products for developing nations have also come to market, including the first new drug in 40 years for multi-drug resistant tuberculosis (Johnson & Johnson), a child-dose HIV tablet (also Johnson & Johnson) and a new pill that can cure hepatitis C (Gilead). The conditions seeing most attention are lower respiratory infections, diabetes, hepatitis, HIV and malaria. Neglected tropical diseases are also a little less neglected than they were a few years ago, and more than half of the companies in the index are developing pediatric versions of medicines.

However, ranking well in the Index is not just about how many relevant products you have; it's more about what you do with them. The Index notes that companies are paying more attention to people's ability to pay, and exploring new business models that facilitate access to medicines in poorer countries, for example, issuing licenses that allow generic versions of drugs to be distributed in developing countries.

Despite all this positive action, the Index identifies two key areas where the industry is lagging behind. Firstly, the Index notes that companies are still "conservative" in their approach to patents and tend to be cagey in revealing where patents are active and when they will expire. An example of this situation can be seen on page 12 where Sandoz was unaware of a patent protecting an Amgen product. Secondly, all but two of the companies in the Index have been involved in cases related to ethical marketing, bribery or corruption in the last two years.

Overall though, the picture is one of incremental improvement. As Leereveld told The Medicine Maker, "These companies are like oil tankers; an oil tanker can change direction, but only a few degrees at a time. We must be patient. I am convinced that companies are making positive long-term decisions." *SS*

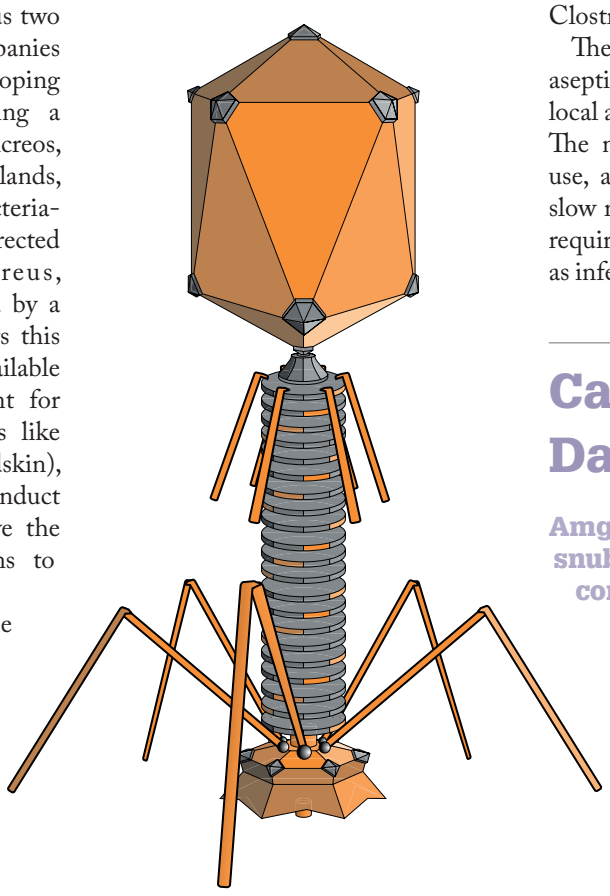
Battle of the Superbugs

Can phage endolysins revolutionize the way bacterial infections are treated – and prevent drug resistance?

We discussed the problem of antibiotic resistance at length in our previous two issues – and while several companies are rising to the challenge of developing new antibiotics, some are taking a different approach entirely. Micreos, a biotech based in the Netherlands, has developed what it calls a "bacteria-killing enzyme": Staphefekt, directed against Staphylococcus aureus, including MRSA. It is produced by a bacteriophage, a virus that targets this bacterium. It has just become available as an over-the-counter treatment for S. aureus-related skin conditions like eczema, rosacea and acne (Gladskin), but the company is looking to conduct clinical trials and eventually have the product prescribed by physicians to supplement antibiotic treatment.

"In nature, phages infect the bacterial cell in order to multiply. After new phages have been assembled, the bacterial cell wall is destroyed by phage enzymes called endolysins to allow the newborn baby phages to be released. With Gram-positives, endolysins work from the outside as well," explains Bjorn Herpers, a clinical microbiologist who tested the drug at Public Health Lab, Kennemerland. "Staphefekt is composed of two parts of naturally existing phage endolysins: one part is best at specifically binding S. aureus, the other part is best at disrupting its cell wall."

One of the main advantages of the technology is that it can eliminate bacteria without causing drug resistance. As the release of the new phages from the bacterial cell is a part of the phage lifecycle, natural selection has yielded endolysins that target highly conserved structures in the bacterial cell wall that cannot easily be changed. According to Herpers, if bacteria could develop resistance to current endolysins, they would have done so already.



However, this doesn't mean the war on superbugs is over. Endolysins are large molecules that cannot enter tissue cells. Since they also harbor natural epitopes, immunogenicity could come into play with systematic administration.

"For local application, for example in burn wounds, surgical wounds, or infected implants, this is much less of a barrier," says Herpers. "The introduction of the first endolysin for human use marks the realization of a technological platform for the development of more endolysins and other fields of phage technology, with lots of potential to target other bacteria, like Clostridium difficile."

The company has also developed an aseptic liquid formulation suitable for local administration in research settings. The next step will be registration for use, and the team is also working on slow release systems for conditions that require continuous local treatment, such as infected implants. *SS*

Care to 'Patent Dance'?

Amgen accuses Sandoz of snubbing its advances in a complex biosimilar dispute

Sandoz's biosimilar version of Amgen's Neupogen (filgrastim) is expected to be the first biosimilar to be approved in the US, but not if Amgen has anything to say about it; it's suing Sandoz for refusing to follow rules laid out in the Biologics Price Competition and Innovation Act (BCPIA). The complexity in the case lies in the fact that the companies are interpreting the rules in different ways – and the result of the lawsuit could serve to shape the US landscape for biosimilars.

Amgen says that the BPCIA required Sandoz to disclose its FDA application and manufacturing information to the

innovator within 20 days of filing. The aim of this process is to let the innovator dig through the information to check for any potential patent disputes – regulatory bloggers have nicknamed it the 'patent dance'. But Sandoz has a different interpretation; it claims the information disclosure is optional. The company did offer to share limited information under certain terms, which Amgen refused. In response, Sandoz said it wouldn't be sharing anything at all, leaving Amgen all alone on the dance floor, so to speak. Amgen has now filed a lawsuit in California and has submitted a citizen's petition to the FDA, in which it describes Sandoz's conduct as "pernicious".

The lawsuit accuses Sandoz of patent infringement, unfair competition and conversion. An article from law firm K&L Gates says that the conversion aspect is particularly interesting since it's not commonly seen in this context (1). It refers to treating someone else's property as your own. "In particular, Amgen asserts that Sandoz's biosimilar application uses Amgen's prior demonstration of the safety, purity, and potency of Neupogen without Amgen's permission and without satisfying the BPCIA procedures," says the article.

Sandoz's biosimilar launch could now be delayed by several months. Amgen is asking the court to prevent the launch of the biosimilar and to stop the application from moving forward at all until the dispute is resolved. In addition, Amgen wants the court to rule that Sandoz can't notify Amgen of its intention to launch the biosimilar until after FDA approval has been granted.

This isn't the first time that the two companies have butted heads over biosimilars. In 2013, Sandoz asked a US court to rule that a biosimilar version of Amgen and Roche's Enbrel (etanercept) wouldn't infringe certain patents. Sandoz had been developing its biosimilar so that the planned launch would coincide with patent expiries, but was caught off guard by other patent applications that it claimed were unpublished and not publicly available. The court ruled against Sandoz, saying that patent litigation couldn't be initiated unless the biosimilar application had already been filed with the FDA. *SS*

How would you interpret the BCPIA? Let us know by commenting online at www.themedicinemaker.com.

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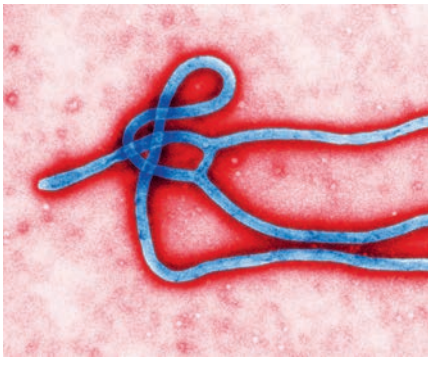

Regulators Target Ebola

Will FDA fast review and voucher incentives make a difference?

US senators are working to introduce a bill to encourage pharma and biotech companies to develop new treatments and vaccines against Ebola. Specifically, the bill would add Ebola to FDA's priority review voucher program, first introduced in 2007. The program incentivizes the development of medicines for neglected tropical diseases. As well as providing faster review of the qualifying medicine, the FDA also awards a priority review voucher to the developer, which can be used for any other product, whether qualifying or not.

The vouchers can also be sold, but only once, and overall they are considered less valuable than vouchers offered through other FDA programs, such as the FDA's rare pediatric disease voucher program (one of which was sold by BioMarin for $67.5 million earlier this year). Vouchers obtained through the neglected tropical diseases program can only be redeemed by giving the FDA 365-days' notice and have rarely been used by companies. Therefore, critics are dubious as to whether adding Ebola to the list will have a positive – or any – impact (1). Especially as it could be months before any Ebola drug is eligible for the scheme since companies must first receive full approval for their investigational new drug application. Sixteen diseases currently qualify for the program, but Ebola is not one of them since previous outbreaks have been sporadic and the death toll lower than diseases like cholera, malaria and tuberculosis.

Meanwhile, Europe is also trying to spur development; the Innovative Medicines Initiative recently issued a €280-million call for projects to boost European research into Ebola. The funding will cover "urgent action" to address the current epidemic and a long-term strategy for managing future outbreaks. *SS*

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Dosing to Circadian Rhythm

Could medicines be made more effective with better timing?

Zhang and colleagues have published an 'atlas' that maps the 24-hour patterns of expression for thousands of genes in different mouse organs (1). They also looked at the potential effect of the circadian clock on medicines and drug development; an examination revealed that the majority of bestselling drugs target proteins made from genes whose expression changes throughout the day. The data have been made publically available through the CircaDB database. John Hogenesch, a professor at the University of Pennsylvania's Perelman School of Medicine, and lead researcher on the project, tells us more.

What inspired this study?

After the human genome project, it was clear there were only about 25,000 genes. After finding the genes, the first thing we wanted to know was where and when they were expressed. At Novartis, to get at this question, we did a large-scale 'atlas' of human, mouse, and rat gene expression in around 80 different organs. This became a public resource that is still used today - in Wikipedia or BioGPS. I was also interested in circadian time back then, but it wasn't until this study that I have been able to more fully explore it.

What does your work tell us?

It tells us just how prevalent circadian clock influences are on physiology and behavior. We found that 43 percent of protein encoding genes are under clock-control in at least one tissue – and we estimate that 55 percent of the genome will be found to be clock controlled once all organs are analyzed. Surprisingly, we also found that almost 60 percent of drug targets were clock regulated. Many of these drugs have short half-lives and are taken as once-a-day formulations, meaning there is potential for time-of-day dependent metabolism or efficacy. For some medicines, such as low-dose aspirin, statins, and angiotensin receptor blockers, it's known that time of day of dosing can have an impact on efficacy.

What are the implications?

At the very least, I hope it will emphasize to everyone that the time of dosing can be important. For example, short-acting statins should be taken before bedtime; it's right there on the label. But one in six patients still take them in the morning.

When it comes to drug development, many companies are focused on long-acting formulations. One implication of clock regulation is that this longer exposure might not be better. If the system evolved to respond in a particular window of the day, putting your foot on the gas 24/7 might not be optimal. These issues need to be considered on a target-by-target, drug-by-drug basis.

What next?

We want to look at drugs with the biggest potential for time-of-day dependent effects – high-amplitude cycling of targets, their metabolizing enzymes or transporters – in organ systems of interest. We will use animal models to provide evidence supporting clinical studies to see if these already relatively safe and efficacious medicines can be further optimized. The payoff here could be huge: new drugs are expensive to develop and fail more often than not. These drugs already work. We want to see if they can work better with optimal timing. *SS*

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The Monoclonal Milestone

The launch of the world's first biosimilar monoclonal antibody was a big step forward from a regulatory and scientific standpoint. Will there be enough room at the table?

By Carsten Brockmeyer, CEO, Formycon AG, Martinsried, Germany.

The market size for monoclonal antibodies (mAbs) is huge. Over the past 10-15 years mAb medicines have become a cornerstone of treatment for chronic and life-threatening diseases, such as rheumatoid arthritis and cancer. Looking at the top ten bestselling medicines worldwide, seven are biologics and five of those are mAbs. There is no doubt that mAbs are highly important drugs that have provided new options for some major unmet medical needs. But they are also very expensive medicines in many cases, which has a significant impact on healthcare costs.

The scale of the market makes last year's European approval of two biosimilar versions of infliximab a real milestone for the biologics industry. Biosimilars typically deliver savings of 20-30 percent – money that could be used to fund further innovation. Of course, we're dealing with large, complex molecules with multiple mechanisms of action, so prices aren't going to match those of small molecule generics. But as more biosimilars emerge over the next couple of years, we can expect to see costs fall further as regulatory and scientific confidence grows. My hope is that reduced costs will not only benefit overstretched healthcare systems here in Europe, but also make these drugs more accessible to the emerging and unregulated markets – that is to say, the remaining 85 percent of the world's population...

The big question is, which kind of companies will come out on top as the market expands? In the late 1990s and early 2000s, big generics companies were the trailblazers in the biosimilar space. But in 2010, when President Obama signed the Patient Protection and Affordable Care Act and the biosimilar regulatory pathway opened up in the US, everyone wanted to jump on the bandwagon, with big pharma and even small biotechs getting in on the action. Most big pharma companies have a generics arm and see this as a strategy for growth and differentiation – after all, if you can't beat them; join them. Large generics companies, seeing that the small molecule market has slowed in recent years, see difficult-to-make generics like biosimilars, small-volume injectables and inhalable drugs as a way of setting themselves apart from smaller competitors who lack the extensive know-how, investment and capacity required. Given an estimated cost of €70-100 million, there are few smaller companies who can take a biosimilar all the way from development to market. Instead, biotechs will generally develop

"The big question is, which kind of companies will come out on top as the market expands?"

"One positive side effect of the growth in biosimilars is that it presents a great opportunity for the European pharma industry."

biosimilar molecules up to Phase I, before passing them on to a bigger company to commercialize. We have seen some new biotech companies being launched over the last few years by 'veterans' of the field, who were involved either with the development of originator molecules or with the first biosimilars. In my view, there is room for all parties at the table; bigger generics and pharma companies will bring biosimilars to market, with some of the earlier work being performed by smaller biotech companies.

One positive side effect of the growth in biosimilars is that it presents a great opportunity for the European pharma industry. In the first half of the last century, Europe was the pharmacy of the world. But in the 1980s and 1990s, low-cost manufacturing in Asia and greater availability of venture capital funding in the US eroded that position. Now that these blockbuster biologics are coming off-patent, a significant market has opened up again – everyone who has the know-how and resources can develop high-quality versions of these products. Europe even has something of a head start, as the US has been slower to implement a regulatory pathway for biosimilars. That said, the US is catching up fast, and the next highly anticipated milestone in the biosimilars industry – the first FDA approval – is potentially just months away.

Calculate – Don't Estimate – Drug Development Costs

Researchers estimate the cost of drug development at over $1 billion, while others say it's less than $100 million. Who's right? And how can we accurately determine the true costs?

By Ayman Chit, Director, Health Economics, Modeling and Market Access, North America and Director, Medical and Scientific Affairs, Canada, Sanofi Pasteur, Toronto, Canada.

In one much-publicized publication, researchers estimated the cost of developing a new molecular entity (NME) in to be in the order of $1.8 billion (1). But is this overstated? Critics say yes, with some claiming that development costs are actually well under $100 million. We clearly have a polarizing debate on our hands regarding the "true" cost of developing new pharmaceutical drugs. One reason for the controversy is that most cost-of-research-and-development (R&D) studies are not reproducible. A recent review article noted that 10 of 13 cost-of-R&D studies were based on self-reported, unaudited and confidential data from unnamed companies and unnamed products (2). The non-reproducible aspects of these data raise questions about how representative R&D cost estimates really are. And we can also question the value of estimating average drug R&D costs at all given the substantial heterogeneity within a single therapeutic area. For instance, the average expected cost of developing an oncology medicine is $1.042 billion, while the cost of developing a medicine within this class – drugs that treat breast cancer – is $0.61 billion. In this case, the narrowly defined R&D cost would be more informative for decision making around new investments in breast cancer drugs.

"The non-reproducible aspects of these data raise questions about how representative R&D cost estimates really are."

My colleagues and I wanted to get to the bottom of the cost question. In a recent study, we demonstrated that the true expected cost of developing a specific pharmaceutical product can be reproducibly estimated using publically

"We know that the majority of the clinical development was paid for by corporations, but it's not clear who funded the pre-clinical research."

accessible data (3). Our method utilized Trialtrove, a database held by Citeline. The database is primarily built on data from clinicaltrials.gov, which has emerged as the go-to posting website for pharmaceutical firms.

Information required in publicly disclosed clinical research programs includes sponsorship, the identity of the investigational product and study design, such as phase, number of subjects, length of study, number of centers and primary endpoints, and more. Using these data, we were able to avoid the selection biases that may have contaminated other cost-of-R&D studies, while also obtaining information on the quantity of the "inputs" used to conduct the R&D – the number of subjects, the number of measurements per subject and study duration. Unfortunately, these data are silent on the unit costs of these inputs, so we obtained cost estimates from a well-known research group.

For the class of products we looked at – seasonal influenza vaccines – we estimate the cost of developing a new product to be around $420 million at a nine percent cost of capital rate. Cost of capital adjustments are needed to account for opportunity cost, since the money could have been used in a different investment with comparable or lower risk of failure. Therefore, the cost of development is highly dependent on who pays for the work. Generally speaking, governments have a lower cost of capital than private and public corporations. We know that the majority of the clinical development was paid for by corporations, but it's not clear who funded the pre-clinical research.

Recently, Parker and colleagues (4,5) reported on the success rates of new drug clinical development for very specific indications: Crohn's disease and Non-Hodgkin's Lymphoma. But the researchers were not able to look at costs. Our project presents a usable method for all researchers – and new estimates of the cost of drug development should help reconcile some of the political debate about current estimates. Additionally, I believe that quantifying development cost estimates for a vaccine or medicine can make investment more attractive, as it reduces the high uncertainty associated with such decisions.

One of the next steps should be to develop an appropriate analytical framework for decision makers. Such a framework should evaluate development costs, anticipated technology impact and overall disease burden. Finally, further research should also focus on how development costs should inform pricing, especially now that payers are moving towards the adoption of cost-effective medicines and vaccines based on fixed price ceilings.

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Sharing Data – and Knowledge

How to use a knowledge repository that doesn't retire or leave you for a competitor.

By Steve Thomas, Investigator, GlaxoSmithKline, Ware, UK.

Millions of dollars have been invested to harness data for intellectual property protection and regulatory purposes, but the industry is severely lacking systems that re-use the data generated in analytical laboratories on a daily basis.

"Organizations still rely on scientists' brains or interpretations scribbled on paper spectra."

In fact, many organizations still rely on scientists' brains or interpretations scribbled on paper spectra when it comes to analytical data and knowledge, even though far more data is generated than can possibly fit in a person's head.

My colleagues and I are responsible for studying the metabolic fate of molecules in development for GSK's drug metabolism and pharmacokinetics department. We generate and consume a lot of data (analytical, structural and species specific) to build metabolite schemes that help us to understand the fate of molecules. Until a few years ago, a lot of our data were recorded on paper, so when I tried to discover if anything similar had been seen in another project or species, I had to ask colleagues or search through the paper files. I also had colleagues in the US, so sharing data in the days of paper records was extremely difficult, particularly as they used software to store analytical data, but not to map metabolic outcomes. I suspect you'll find a similarly fragmented approach to analytical data in other global companies.

Quite often the terms 'data', 'information', and 'knowledge' are used indiscriminately and interchangeably, but an understanding of these terms can help you identify where you have a gap.

- Data is raw and represents a set of discrete facts; it has no significance beyond its existence.
- Information is data that have been processed to derive meaning and purpose.
- Knowledge is the human understanding of the subject matter, acquired through study and experience, which helps us draw meaningful conclusions.

These terms form an ascending scale of value and context. The following metaphor makes the difference clear. Out shopping, you might spot an old colleague. The facial recognition represents data. The value is increased by information or metadata that begins to fill in the picture. You remember his dog's name and what his daughters were studying in school. Knowledge is how you recall that he is dreadfully dull! You quickly duck into a store to avoid him, thus using your acquired knowledge to guide your actions to a preferable outcome.

"Knowledge is the human understanding of the subject matter, acquired through study and experience, which helps us draw meaningful conclusions."

Several years ago at GlaxoSmithKline, we set out to create a repository of knowledge that doesn't forget, doesn't go senile, doesn't retire, and doesn't leave the company for a competitor. Our goal was to capture spectra generated in sample investigations, as well as the context (associated metabolites, and project details) and insights associated with the data (interpretation and conclusions drawn), so that our investigators could share information easily and learn from past outcomes. The end result was very positive and allowed us to better manage our knowledge, which is why I am sharing it here.

Our solution was to implement software from ACD/Labs that could store, search and share analytical and metadata linked to structures in a biotransformation map. We were able to collect analytical data from different techniques (mass spectrometry and nuclear magnetic resonance are widely used in our research); connect it with metabolite structures and other information; and map the data onto biotransformation schemes that record the metabolism pathway, where the parent drug can turn into 100 metabolites. Importantly, it was a way of sharing data with colleagues worldwide so that we could all benefit from previous experiences when looking to develop compounds that could avoid a particular metabolic fate. The data could be searched from almost any facet; for example, by molecular mass, project, analyst, site, species, or structure. Sharing data is extremely important because access to colleagues' findings can give you confidence in your own conclusions, or reveal additional considerations when analyses have proven tricky.

We've configured the software to fully meet our needs and it's also provided other benefits beyond access to information. Reports that used to take weeks to compile, requiring cut and paste from various vendor software and data management silos, can now be created much more easily.

We haven't looked back, but I can see why others in our industry may be wary. Even when a new technology or piece of software offers benefits, the pharma industry is cautious of change, after all there is a mentality of: "if it ain't broke, don't fix it" – the change curve could bring about a dip in productivity. But many companies are perhaps unaware that if they don't facilitate the sharing of data and knowledge, they are already experiencing lower than optimal productivity.

What About the Kids?

Since the late 1990s, new regulations have given us the opportunity to address the needs of the most vulnerable and demanding patients – children. Making medicines for pediatrics adds a whole new dimension to the challenges of formulation and drug delivery, but as our knowledge expands, exciting new developments are in the pipeline.

By Jenny Walsh

Historically, drugs have been developed, tested and authorized for adults only. Most people would agree that children have a right to safe, effective medicines, suitable for their needs, but translating this into practice has been a slow process.

In most cases, developing pediatric medicines has not been financially appealing. Developing pediatric drugs is often both costly and risky, and the target market may be only a handful of children, which makes return on investment questionable. The result is that very few products have been specifically developed for children; clinicians often have to rely on off-label or unlicensed drug use, and extemporaneous preparations such as crushing tablets and mixing them with water to administer what they hope is the correct dose. However, with new directives pushing the issue into the spotlight, the last ten years have seen an increasing focus on the needs of children in the drug development process.

Indeed, regulations in the US and Europe now require pediatric plans for all new patent protected drugs, including line extensions, with incentives in the form of extended exclusivity. The regulations have certainly had a significant impact, but it is only now that we are starting to see the results, with new pediatric drugs hitting the market and the industry gaining experience and confidence. There are still major challenges, but I believe we're going to see great advances in the coming years with the continued commitment of academia, governments and industry.

How is developing a pediatric medicine different to developing an adult drug? In fact, the general principles are exactly the same. The key differences lie in safety and acceptability. It is often said that children are not just small adults, and new research is teaching us just how true that is. During infancy and childhood there is rapid growth and changes in various organs, body composition and metabolic pathways. There are also differences in gastric pH and gastrointestinal motility between adults and children. This means that babies, infants and children may handle excipients and active pharmaceutical ingredients (APIs) differently, leading to potential toxicity and changes in the required dose of API.

Here, I discuss the main areas to consider when developing pediatric medicines, and look at how far we've come since the regulations came into effect.

Children take center stage

Recognizing the lack of pediatric formulations entering the market, and the limited availability of information on the safe use of medicines in children, both the US and Europe introduced new regulations in the late 1990s and 2000s to tackle the problem. The regulations include a 'carrot and stick' approach, with requirements for pediatric development plans for patent protected products offset by an extended exclusivity period. There are also incentives in place for the development of off-patent pediatric medicines. Read more in "Taking the Guesswork Out of Pediatric Medicine."

In Europe, since 2007 all companies developing a new product, or a line extension for a patented drug, must submit a pediatric investigation plan (PIP) to the European Medicines Agency (EMA) Pediatric Committee (PDCO) no later than completion of adult human PK studies (after Phase I trials). The PIP is a plan of work and should contain preclinical information including juvenile toxicity studies, details of the proposed pediatric product and the clinical trials to be carried out in the pediatric population. Validation of the adult licence application is conditional on companies complying with the agreed PIP, which also gives them a six-month extension of their supplementary patent certificate.

Regulators are clearly keen for drug makers to consider the needs of the whole pediatric population, including neonates (newborns). However, from a company perspective, it is risky to spend time and money working on pediatric indications of a drug that may never come to market – and so some companies are delaying pediatric development. The EMA has quoted several cases where PIPs have been submitted during Phase III adult trials, and found to be totally unsuitable. The companies have then had to re-formulate the product or re-do a clinical study, causing considerable extra expense and delay. I think the message is very clear – pediatrics should not be a bolt-on, but an integral part of our drug development processes. There are several key building blocks in particular that need to be carefully considered.

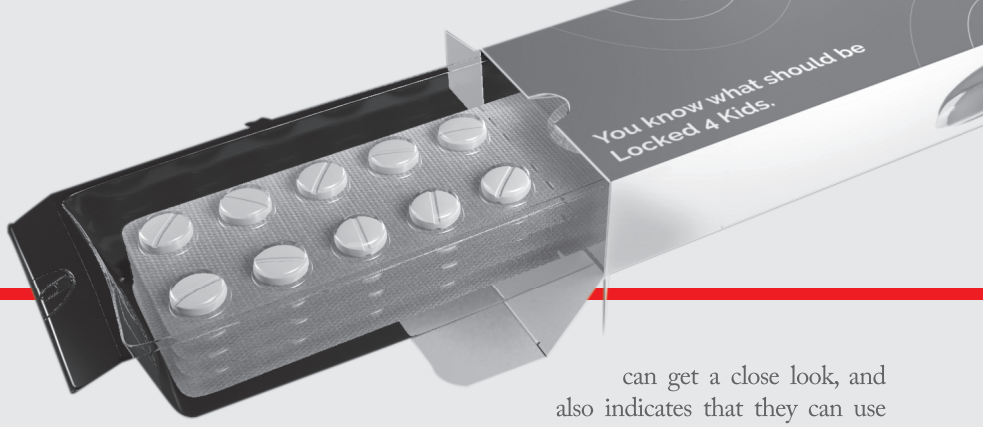
"Pediatrics should not be a bolt-on, but an integral part of our drug development processes."

Safety first

Finding excipients with appropriate safety and tolerability is a major hurdle in pediatric drug development, and we have to justify the choice of excipients in the PIP. The immaturity of organs, particularly of very young children, mean that certain excipients can't be metabolized in the same way as an adult. A classic example is that high doses of propylene glycol, a common additive in food and medicinal products, can be toxic for babies. So it's important to look at the absorption of these materials, how they're broken down, and whether there is the potential for them to accumulate.

There are a lot of older medicines currently used for children that would not get approved via the current regulations. A study carried out in 2009, looking at commonly administered liquid medicines, found that levels of excipients such as ethanol and sorbitol were potentially harmful for premature infants, and were above recommended levels for adults on a weight basis (1). The authors estimated that the dose of ethanol might be equivalent to giving the babies several beers per week!

What makes our lives so difficult as drug developers is that there is limited information available about the safety of excipients for pediatric patients, especially in very young children. In general, the aim is to use as few excipients as possible and to stick to those with a well-established safety profile. Each excipient should be assessed by considering the benefit versus risk of its use, weighing up a range of factors, including the age of the patients, how long they will take the medicine for, the indication, what dose they will receive and if there is an alternative excipient. For example, if the product is for the treatment of a life-threatening condition (e.g. cancer) it might be acceptable to use an excipient that has limited safety information to increase



Masters of Destruction

Medicine poisoning in children is a common occurrence, particularly in children under five. In the US alone, a child is taken to the emergency room every eight minutes due to poisoning with a medicinal product. Most medicine bottles come with child-resistant (CR) caps, but to date there have been few products available to keep children away from blister packs, which make up 80 percent of drugs in Europe. Making a carton that can withstand a determined 4-year-old is no easy task. Ron Linssen, Managing Director of packaging development company Ecobliss, explains how they did it with Locked4Kids.

What are drug companies' responsibilities with regard to CR packaging?

Legally, Europe lags behind the US. In 1970, the US introduced the Poison Prevention Packaging Act, which forced pharmaceutical companies to use CR packaging for all prescription drugs, as well as various other potentially toxic substances. EU law does not require medicines in blister packs to be supplied in CR packaging, though some member states have limited regulation. According to the WHO, the introduction of CR packaging in the US led to a dramatic decrease in child poisoning, so I think the time has come for the European Commission to review this. Medication use has only increased over the past decade, and tablets can be very appealing to children.

How do you make the carton hard for kids to get into, but easy for everyone else?

It took us almost two and a half years to develop a carton that can withstand all of a child's ingenuity and strength, but is easy to use for adults and the elderly. It is a delicate balance; a tightrope walk. The trick with Locked4Kids is that it requires virtually no force to open. You just have to press two points on the carton and pull the tray out. But the points are spaced so that it is very difficult for young children to push both at once.

What was the toughest part of the process?

The most difficult thing is to get the product through child testing. Each test is done with 50 children aged around three or four. They initially get five minutes to do whatever they want to try to open the packaging; then the tester, without speaking, demonstrates how to open the packaging. He or she does this about two feet from the kids' noses, so they can get a close look, and also indicates that they can use their teeth to get it open if they want. Then they get another five minutes. Now, for children this age ten minutes is a long time, and watching the tests, it's amazing that any carton would withstand it! The children will try to poke their fingers in, pull as hard as they can, squeeze it, bite it – anything to get it open. Every time you make a change to the design, you have to go through this testing again. You may think the design is good, but it's the kids who will have the final verdict! And if you make it too hard for the kids, it often becomes too challenging for older patients too, so it's back to the drawing board.

What has the reaction been like so far?

Usually, when you bring out a totally new product, you expect some backlash. But people are responding very positively to this. We have tried to make it easy for manufacturers – Locked4Kids production can be easily automated, and can be used wherever you would use a normal carton. Obviously compared with an ordinary carton, Locked4Kids is more expensive. But compared with a CR bottle the costs are similar. We hope responsible drug companies will consider CR packaging even where there is no legal requirement.

solubility to achieve sufficient bioavailability, whereas the same excipient might not be acceptable for use in a product for a less serious condition (e.g. a cough medicine). The European Pediatric Formulation Initiative is building a database ("STEP Database") to act as a repository of excipient information available in the literature, to assist in the development of pediatric medicines (www.eupfi.org).

Can't take, won't take

Dosage form is a key consideration right from the start of the pediatric drug development process. Small children have difficulty swallowing conventional tablets (especially large tablets), and there is a risk of choking. The WHO reports that four children under 36 months died from choking on albendazole tablets during a deworming campaign in Ethiopia in 2007 (2). The most common solution to this issue is an oral liquid version – along with all the formulation challenges that it can bring. Keeping potential pediatric dosage forms in mind at an early stage of development, for example when selecting the salt for the API, could save a lot of additional work later on.

An interesting development over the last two to three years is that I've seen more interest in solid oral dosage forms, even for

Tiny Babies, Big Challenges

We caught up with physician and researcher Mark Turner, Senior Lecturer in Neonatal Medicine at the University of Liverpool, Director of Research and Development and Honorary Consultant Neonatologist to Liverpool Women's NHS Foundation Trust, to find out more about the unique needs of newborn and premature babies.

Other than their size, what makes children, and particularly babies, process drugs differently to adults?

There are two big reasons that babies handle drugs differently. First, their bodies are maturing and developing. In the liver, most medicines are metabolized via a number of enzymes and children and babies have different enzymes to adults. In the womb, the mother filters out most toxins, but a few make it though and need to be metabolized. So the baby is programmed to protect itself from the chemicals that get through the placenta. As they get older, children face different environmental pressures, so the liver is gradually reprogrammed. These differences in liver enzymes can have unpredictable effects. For example, some of the activity of morphine comes from specific metabolites – since young babies lack the enzymes that produce those metabolites, different doses of morphine may be needed in babies. The second reason is that the targets are different. When you give a drug that works on certain receptors, sometimes those receptors aren't present in children.

How much do we know about those differences?

We probably only know a tenth or a quarter of what we need to know. Ethically, we can't do studies in healthy children, so the only way to find out more is to track the medicines and metabolites in our young patients, which can be challenging. I work with babies who weigh as little as 500g and have a total circulating volume of 30 or 40 ml of blood. Clearly, we can't take the same amount of blood as we do in adults or older children, so we have to adapt our studies.

What challenges do neonatologists face in terms of availability of drugs?

Estimates of the proportion of drugs licensed for neonates vary between 10 and 25 percent, so we often have to use drugs off-label. I describe my job as guessing which drug to give, guessing what dose to give, and hoping the team don't make too many errors as they dilute medicines that are intended for adults. Often the drugs have to be diluted by ten times to give a dose small enough for a baby. The current regulation in Europe and the US will improve this over time for new medicines, but there are a large number of off-patent medicines that are always going to be a problem.

What is needed to improve the situation?

Along with many of my colleagues, I think we need to change the incentives that are available to pharmaceutical companies to evaluate off-patent medicines. Many drug companies want to do the work, but at the moment it is just not economically viable. There needs to be a global discussion with companies, regulators and payers about how we can incentivize the study of commonly used off-patent medicines.

I spend half of my time looking after sick and dying premature babies. I stand at the end of the cot and I have to guess which drug to give and at what dose - the uncertainty is such a burden. That's what motivates me to study drugs and help other people to study drugs - to try to remove some of that uncertainty.

Dangerous Drugs

49% *of drug prescriptions in pediatric wards were either unlicensed or off label, in a 2012 Swedish survey (5).*

3x *higher rate of exposure to potential adverse drug events (ADEs) in pediatric inpatients compared with adults (6).*

79% *of potential ADEs in hospitalized children occurred when doctors were ordering medications (6).*

Over 70,000 *children attend US emergency departments every year after accidental medication poisoning, usually after getting into parents' or grandparents' medication (7).*

20% *increase in children under 5 visiting the emergency department for accidental medication overdoses from 2005 to 2009 (7).*

2 *is the peak age for accidental medication overdose (7).*

63,358 *calls to US poison control hotlines are made every year by concerned parents or caregivers after a medication error at home in a child under six (4).*

1/4 *of medication mistakes occurred in infants under one (4).*

1/4 *involved the child being given the same medication twice (4).*

"It is not uncommon for parents to inadvertently over or under-dose their child's medication."

very young children. Oral liquids have historically been the preferred dosage form for pediatrics – and I think there is still a very important place for them in terms of dosing flexibility – but there are concerns about the preservatives required. In resource-poor areas, stability, transport and storage of liquids may also be an issue. There seems to be an increasing trend to use powders that can be dissolved or dispersed in water just before taking, to make solutions or suspensions. The development of oral films, orodispersible tablets and mini tablets is also becoming more common. These mini tablets are just two or three millimeters in diameter. It is generally accepted that a child would need to be about six to be able to swallow a conventional tablet, but this depends on the size of the tablet and the ability of the child. Studies published in the literature have successfully administered mini tablets to infants aged as young as six months, so this could be an exciting area in the future (3).

But of course, just because children can take their medicine doesn't mean that they will do so willingly! Children are typically less tolerant of the bitter taste of many APIs and prefer a sweeter taste. This isn't just children being difficult – there are subtle differences in how children and adults perceive tastes. Something that an adult might say was a slightly bitter, a child may find genuinely disgusting, and so companies take taste of pediatric medicines seriously. Quite a few companies use an 'electronic tongue' as a screening tool to make an initial assessment of the bitterness of their APIs and formulations. This gives an idea of what taste-masking, if any, is required. Palatability of formulations may be assessed using a taste panel, or during clinical trials. Clinical studies now often include a questionnaire asking participants about the taste and texture of the medication, and this is particularly important in pediatric trials, as it's very difficult to directly extrapolate adult taste panels to children. There is currently no standard methodology for conducting palatability and acceptability studies, and this is another area of future development. Of course, there is a fine line between making a medicine palatable and making it too nice, which encourages children to view the medicine as sweets...

Delivery dramas

The delivery device can also play an important role in the safety and acceptability of children's medicines. It is not uncommon for parents to inadvertently over or under-dose their child's medication, as they can find measuring the right dose difficult. According to the results of a recent US study that examined 11 years' worth of records from the National Poison Database System, a child experiences a medication error every eight minutes, and while the majority didn't require treatment, 25 lost their lives (4). In an effort to make dosing easier for parents, several companies are now looking at fixed-dose oral syringes, with a locking mechanism that allows the dose to be set by a pharmacist, for example.

For older kids, there are some innovative designs in the area of pen injectors for insulin or growth hormone that try to make them less like medicines and more fun. For example, there are some devices shaped like cars. The idea is to make kids less embarrassed to carry them round in their pockets and to use them if needed.

In adolescents, compliance for a chronic condition is notoriously bad, so anything that makes it easier or less embarrassing for this age group to take their medication is very welcome. Teenagers are less interested in car-shaped devices, but there has been a lot of discussion around discreet packaging, such as small packs with one or two doses that can be slipped into bags or pockets. So far, though, we've seen few actual innovations. Things are further along in the over-the-counter market, with some of the major painkiller brands bringing out interesting small wallet packs, so it would be great to see prescription pharma use some of these platforms.

Growing up

In Europe, over 1,600 PIPs have been submitted, but there is a significant lag time before the products come to market as the majority are still in development. So, hopefully further down the line we will see a lot more pediatric products, including more off-patent products. Whilst new drugs now have to consider a pediatric formulation, many existing off-patent drugs are still being used off-label – a situation that has been difficult to remedy given the potential poor return on investment. In Europe, regulators have introduced an

Taking the Guesswork Out of Pediatric Medicine

We have seen more studies conducted in children in the past seven years than we have in the last 30 combined. This is in part down to new rules and incentives introduced in the US and Europe in the late 1990s and 2000s to address the neglect of children in drug development, so that physicians are not forced to rely on off-label use.

United States

Pediatric medicines in the US have not one, but two specific Acts. In 2002, earlier legislation was replaced by the Best Pharmaceuticals for Children Act (BPCA), which offers an additional six months of patent protection for companies who agree to carry out pediatric studies requested by the FDA. BCPA is voluntary and acts as the carrot for drug companies. The stick comes in the form of 2003's Pediatric Final Rule and Pediatric Research Equity Act (PREA). Under PREA, companies submitting new drug applications to FDA must include a proposed pediatric study plan, which is similar to a PIP, but generally submitted later, at the end of Phase II. In certain circumstances, the law also allows FDA to require pediatric assessments for drugs already on the market. As in Europe, it is possible to defer submission or to obtain a waiver.

PREA and BPCA were re-authorised under the FDA Amendments Act (FDAAA) in 2007 and then were permanently re-authorised under the FDA Safety and Innovation Act (FDASIA) in 2012.

Europe

The European Medicines Agency (EMA) has introduced various documents and directives concerning pediatric medicine and children in clinical trials since 2001, but most companies chose not to pursue development in this area. In January 2007, however, the Pediatric Regulation came into force, which made pediatric studies mandatory for all new medicines.

The plan must contain a full proposal of all studies and timings needed to support pediatric use in all necessary age-appropriate formulations, and must be approved by the EMA's Pediatric Committee. Modifications can be made at a later stage as knowledge increases through development and, of course, not all new drugs are suited (or needed) for children, in which case companies can apply for a waiver from the EMA.

Companies that comply with their PIP receive an additional six months of patent protection. The EMA has also been keen to encourage drug makers to pursue pediatric formulations for off-patent drugs. This process is voluntary and also requires the submission of a PIP. Once approved, you can use the PIP to apply for a Pediatric Use Marketing Authorization (PUMA), which is a license to use a product in children only. The reward for this is ten years of regulatory data and market protection.

incentive: companies that obtain a Pediatric Use Marketing Authorization (PUMA) for an off-patent medicine receive an additional ten years' data exclusivity. However, only one PUMA has been granted to date, and most research on off-patent drugs is being done by small companies, the European funded consortia and academia. This may be in part due to the uncertainties that companies face in the reimbursement of these medicines.

As companies and regulators gain experience and more products become available, our understanding of the unique needs of children will only grow. We will also benefit from research being carried out on the physiology and pharmacology of children in different age groups – it is encouraging to see our collective knowledge expand.

The next big challenge for researchers in this area is to address the neonatal group – babies are almost like a different entity because there are so many changes in terms of organ development, enzyme maturation and so on, in that first year. Companies need to do more research in this group, despite the caution that is natural when working with tiny babies (see "Tiny Babies, Big Challenges" for the neonatologist's view).

Working with pediatric drugs is always a challenge, and sometimes unpredictable, but it's that extra dimension that makes it so fascinating.

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Connecting the Dots in Drug Delivery

The days of "low-hanging fruit" in drug discovery are a thing of the past. Drug candidates are increasingly made up of complex, poorly soluble molecules – and that poses a big challenge: how can we continue to produce effective medicines that meet patient needs?

Welcome to the first part of a four-article series that will explore the unprecedented challenges facing pharmaceutical scientists – in particular, the ability to offer good bioavailability and patient-friendly drug delivery for increasingly complex new medicines. Over the coming months, we will review the current and emerging technologies that are likely to play a role, discuss the need for a more collaborative approach, and speculate on the future of drug delivery in an attempt to connect all the dots.

The high fruit

"There has been a significant trend over the last 10-15 years for more and more lipophilic drug candidates. Up to 70 percent of new drug candidates now belong to what's called BCS class II, meaning low solubility compounds with high permeability," explains Ralph Lipp, a pharma consultant and founding advisory board member of Catalent's Applied Drug Delivery Institute (see "Running the Institute" on page 30). "These compounds are often difficult to deliver orally as they do not dissolve fast enough during gastrointestinal passage. In general, a drug that is not dissolved cannot be absorbed into the body."

But a reduction in bioavailability isn't the only problem. Poor solubility is also often associated with unacceptable variability in blood levels of the drug, both within and between patients – and it increases the risk of food effects.

Despite the challenges, oral dosage forms (read: convenient and non-invasive) remain the preferred route of administration for traditional small molecule drugs, making up around 40 percent of all prescription drugs (1). In essence, to deliver the convenient dosage forms that patients want, we must find ways to enhance the bioavailability of poorly soluble drugs. To do that, we need to connect more than a few dots...

Simple solubility?

Improving solubility is simple in theory: we (just!) need to break down the crystal lattice structure before the patient ingests the medicine. In practice though, with the demands of stability and patient acceptability to contend with, it's a much trickier proposition. Typically, the lattice can be broken down by applying heat, shear stress or solvents to the API and adding suitable excipients. Hot-melt extrusion or spray drying to create solid dispersions, self-emulsifying drug delivery systems and nanocrystal formation are just some of the techniques available to aid formulation scientists in rendering the insoluble soluble. And new advances are being made every day (2). However, there is no one-size-fits-all solution. What is needed is a toolbox approach – and the more tools at our disposal, the better!

In the midst of all the technological options open to us, it's important that we don't lose sight of our end users. Indeed, we must bear them in mind at the earliest stages of development. It's not just about finding a drug delivery strategy that works, but one that works for patients.

"The first step in patient-centered design is to understand that patients are not a homogenous group but made up of many different groups, often with vastly different needs," says Lipp. "For example, we have an opportunity as an industry to do more to meet the needs of geriatric patients, who make up an increasing proportion of the population." Those needs could include anything from developing easily distinguishable tablets (to avoid negative drug interactions in this highly medicated population) to improving packaging to make life easier for those with rheumatoid arthritis.

Age is just one factor to consider – social, cultural and convenience factors play important roles too, and there are subtle differences between territories. For

example, a tablet mass of over 300mg is considered acceptable by most patients in Europe, but is too large in Japan. Even biologic drugs, which have traditionally been delivered by injection, are moving towards more patient-friendly options, with inhalable, topical and oral dosage forms being explored by researchers (3,4,5).

Team delivery

The diverse challenges involved in creating the best formulations for patients will not be overcome by single organizations, operating in a vacuum. To fill the gaps in our knowledge – and to get the best results for patients – will require input from industry, academia, and equipment and chemical suppliers.

Kurt Nielsen Ph.D., Senior Vice President of R&D at Catalent, believes that knowledge sharing between and within organizations is vital. "Drug development scientists are no different from anyone else – they tend to stick with the tools they know well. Sometimes, that means that progress isn't as fast as it could be if they were using a broader range of drug delivery tools."

Life sciences companies are becoming increasingly aware that precompetitive collaboration is good for business – and for patients. PhRMA Executive Vice President William Chin describes it as a "tide that raises all boats." Companies are already coming together to explore disease mechanisms and identify potential drug targets. To encourage a similar knowledge-sharing approach to speed innovation in drug delivery, Catalent set up the Applied Drug Delivery Institute in 2012. Lipp says his role within the Institute taps into an absolute passion for improving drug delivery for patients. "The Institute's mission is to bring together scientists from both industry and academia, with a goal of moving the needle for drug delivery as a whole – that very much matches my ambitions."

In the following three articles, we'll be exploring some of the most important strategies in the drug delivery toolbox, including the latest advances in existing techniques such as hot melt extrusion lipid-based systems, emerging technologies such as nanotechnology, and cutting-edge research on alternatives to injection for macromolecule drugs.

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Delivering Events

The Journey to Optimizing Outcomes: Advances in Drug Delivery & Design
March 12, 2015
Pfizer Cambridge Campus, MA, USA
Innovative technology companies will present on the following topics:

- Dr. Dave Miller from Dispersol on solubility issues
- Stephen Tindal from Catalent on lipid based drug delivery applications
- Dr. Ben Maynor from Liquidia Technologies on nanotechnology
- Dr. Shahar Keinan from Cloud Pharmaceuticals on data driven drug design

Addressing the Challenges of Drug Delivery: Patient Centric Design, Non-invasive Delivery of Macromolecules, Bioavailability & Solubility
April 30, 2015
3M Customer Innovation Center, Bracknell, UK
Presenters and topics include:

- Dr. Ralph Lipp from Lipp Life Sciences on using patient insights to design drugs and medical systems
- Dr. Mark Tomai from 3M on the use of novel toll-like receptor agonists and delivery systems to increase the effectiveness of vaccines
- Professor Claus-Michael Lehr from the Helmholtz Institute on innovative drug delivery methods

Tech Incubator

The Applied Drug Delivery Institute acts as a technology incubator, offering help to both academic researchers and small companies.

Helping researchers: The Institute acts as a matchmaker, connecting university researchers and their promising technology with companies and experts who can help move their invention toward commercialization, by providing access to facilities, plus strategic and commercial expertise.

Helping emerging companies: The Institute helps start-ups develop their technology by giving them access to the resources and expertise that are typically only available in larger companies, and by helping to identify potential strategic partnerships and funding sources.

Running the Institute

Kurt Nielsen Ph.D., Chairman of the Catalent Applied Drug Delivery Institute and Senior Vice President of R&D at Catalent, shares founding philosophies, objectives achieved and future ambitions.

What's the background to the Institute?

We have a fundamental belief that the pharmaceutical industry should compete on the application of knowledge, not the existence of knowledge itself. By becoming an educator and disseminator of information, we believe we can help expand the industry's toolkit and allow more drug delivery problems to be solved.

We also felt that there was a connection missing between the drug development process and the patient. When a product is being developed, the focus tends to be firmly on clinical efficacy and safety. Making a drug product that is as easy as possible for the patient to take is not usually on the radar at such an early stage. We want to start the conversation about the needs of patients earlier, when the clinical protocols are being developed. In short, we don't want drug delivery to be an afterthought in the development cycle.

Finally, we want to be a connection point, bringing together industry, academia and the healthcare authorities to share information about new technologies and help move them into the toolkit as quickly as possible.

It's a grand ambition – what are you doing to achieve it?

We hold complimentary one-day symposia, organized around a specific drug delivery topic, such as bioavailability or controlled release, with invited speakers from academia and industry to start discussions. Past sessions have all attracted over 100 attendees, including everyone from vice presidents to principal scientists to graduate students. It's an opportunity for scientists to learn, to network and to be exposed to new technologies.

We have also formed working groups and consortia that bring companies and academics together to address key issues. In terms of patient advocacy, we just kicked off a project with the Lung Cancer Alliance to gather information from patients on their feelings about the current treatment regimens. We hope to discover ways of improving their experience.

"We want to start the conversation about the needs of patients earlier, when the clinical protocols are being developed."

Which initiatives are you most proud of?

Our symposia have been a real success; fantastic collaborators, such as the Royal Society of Chemistry, and speakers made sure of that. There have been five so far, but more are planned (see "Delivering Events"). Participants have reported that the content was meaningful and provided a solid opportunity for learning. We have also used their feedback on their most significant delivery challenges as a guide to shape the content of future symposia, which will cover solubility issues, drug release profiles, stability of API and targeted delivery. Ninety five percent of participants believe that drug delivery technology solutions should be determined during pre-clinical and Phase I development. We're also proud of progress made within the Non-invasive Macromolecule Delivery Consortium (NMDC). We're very interested in how we can improve the adherence for these large-molecule injectable drugs. How do you make administration as easy and painless as possible, so that patients don't see taking the drug as such a hurdle? There is real enthusiasm from our collaborators in the consortium, including founding co-sponsors Takeda Pharmaceuticals, Genentech, 3M and Allergan. The more we talk to each other the more we find that the challenges we face are very similar, so it makes sense to work together rather than solve the same problem five times at different companies. We now have working groups set up to address oral, pulmonary/nasal, transdermal and ocular delivery, and efforts are continuing to spread the word and get more and more organizations participating.

What are your plans for the future?

We're particularly enthusiastic about doing more on the education front, and about working to accelerate new technologies (see "Tech Incubator"). We're also really excited about our work with the Lung Cancer Alliance. We want to see patients brought into the development process earlier, so that all the features that lead to maximum adherence can be included in the first generation product, rather than after commercialization. That can only happen when there is data on what patients need, so getting involved with that research is a logical next step for the Institute.

For more information, visit www.drugdeliveryinstitute.com.

Best Practice

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Pass Me a Bottle Opener
Can we unblock the biopharmaceutical bottleneck in downstream processing?

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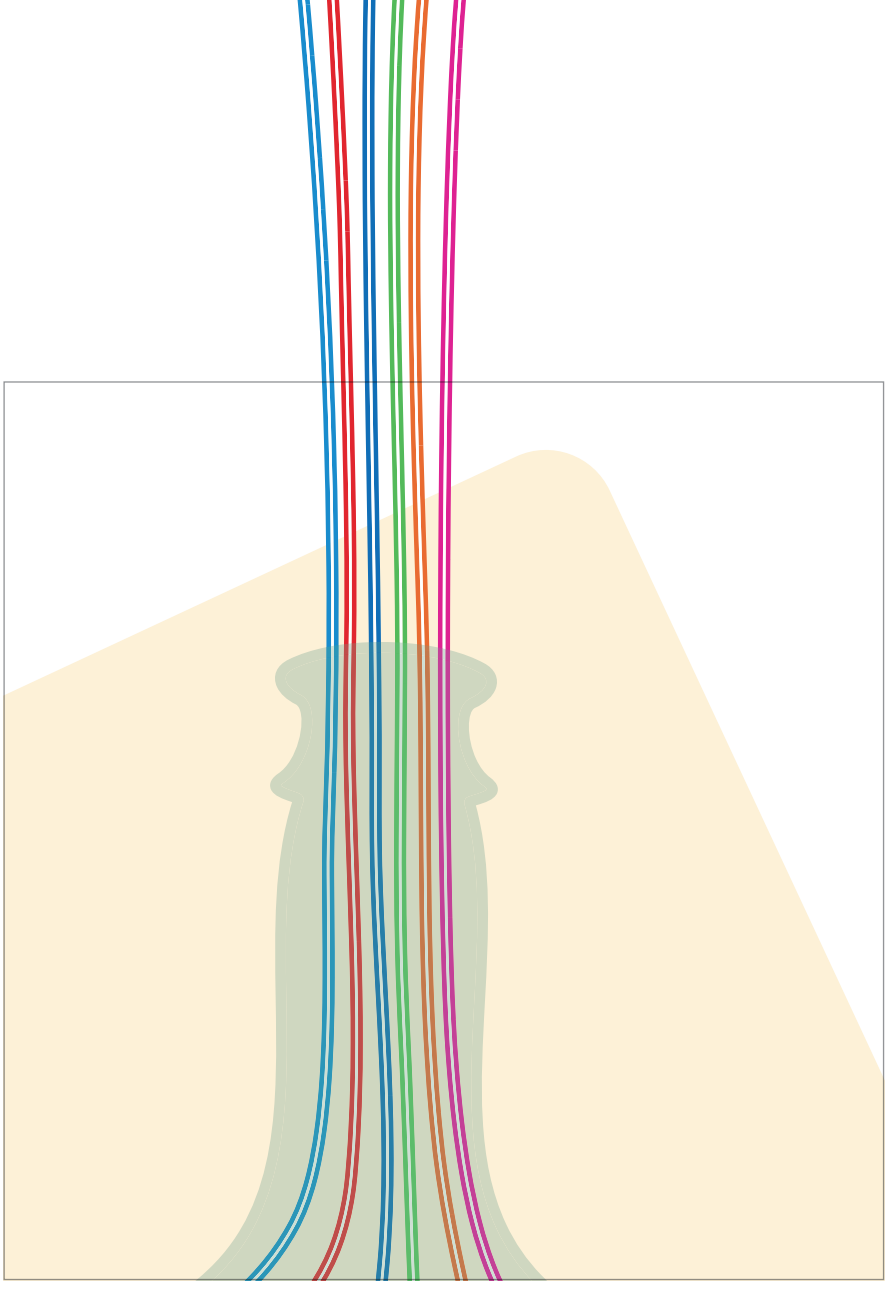
Sizing Up Biologics Side Effects
Biologics present unique safety challenges - add biosimilars into the mix and things get even more complex.

Pass Me a Bottle Opener

Upstream processes in biopharma manufacturing are growing ever more efficient; conversely, downstream processing is increasingly a bottleneck. Can a new generation of chromatography techniques and technologies get things moving again?

By Jaime Marach, Ph.D.



Biopharmaceutical products are manufactured by producing a synthetic or recombinant peptide or protein (upstream processing), purifying and preparing the appropriate pure active ingredient salt form (downstream processing), and then formulating the active ingredient. Historically, upstream processing limited final manufacturing yield and efficiency, but the tide has turned in recent years. Improvements in recombinant production titer and synthetic peptide starting materials have increased upstream yields and instead turned downstream processing into the major bottleneck. In this article, I'll guide you through the pressure points in downstream processing and look at emerging technologies that are clearing the way.

First of all we need a definition. The definition of a biopharmaceutical product varies, but for this article we'll assume that the term encompasses recombinant proteins from living biological sources, such as antibodies or erythropoietins, plus synthetically produced molecules, such as larger peptides, that are sizeable enough to have a secondary structure. Downstream processing may account for up to 80 percent of production costs for these products and the downstream processing equipment market is worth $5 billion per year (1, 2). Increasing the efficiency and output of the process is clearly a priority for all companies in this space.

Whatever the product, biopharma manufacturing companies face similar challenges when it comes to increasing the efficiency of downstream processing:

- Legacy plant design issues
- Capacity of downstream equipment
- Cost and capacity of chromatographic resins and capture steps
- Recent emphasis on quality by design (QbD) and predictive tools
- Increased titers upstream, resulting in disproportionately higher impurity levels
- One-size-fits-all platforms (for example, for antibody purification)
- Time of operations
- Limited options for disposable equipment
- Cost of membranes
- Cleaning and validation costs of downstream equipment
- Expensive chromatography media and filters.

It's a daunting list. The good news is that with so much attention focusing on this area, solutions are beginning to emerge that may help manufacturers

reduce costs and increase throughput.

Figure 1 shows the main downstream processing steps. A whole range of techniques can be used, including centrifugation, pH adjustment, filtration, size exclusion, chromatographic purification and polishing and buffer/salt exchange by ultrafiltration/diafiltration. But there is no question that the workhorse of downstream processing is chromatography, and this has historically been the main target for efforts to boost efficiency.

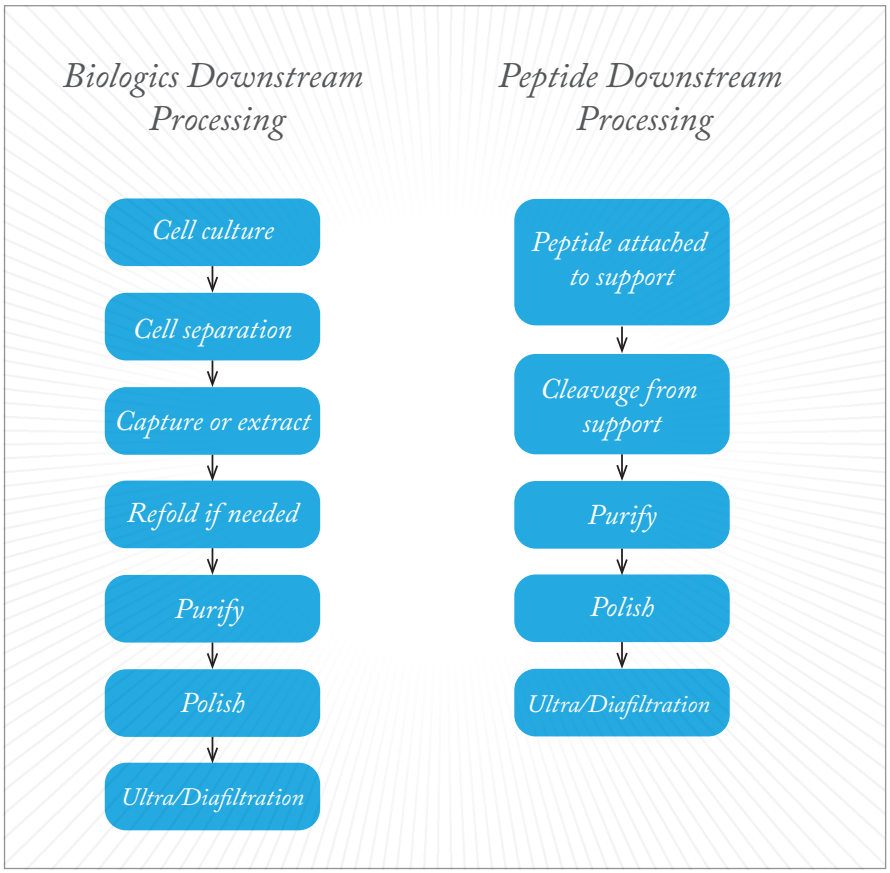


Figure 1. Generalized diagram of downstream processing steps for biologics and larger synthetic peptides .

Knowledge is power

For years, regulatory authorities have been implementing initiatives using principles defined in QbD that aim to increase the quality of drugs by identifying critical quality attributes of the product and process parameters for the manufacturing processes. If we apply these principles to chromatographic purifications, we can use mechanistic models to better design and understand the processes. These models may be built on molecular properties, molecular interactions, chromatographic resin properties, hybrid approaches (a combination of experimental and mathematical models), or simply trial-and-error (3).

The properties of the molecule and its molecular interactions with the chromatographic resin are grounded in the structure of proteins. As a refresher, the primary structure of proteins consists of chains of amino acids, which may associate via hydrogen bonds, salt bridges, disulfide bonds or post-translational modifications into secondary, tertiary or quaternary structure. The properties created from these sequence and structure characteristics affect the interaction with the resin, and can be used to predict chromatographic behavior and, thus, optimize the process.

Model behavior

New process design tools – statistical and mechanistic models that incorporate elements of design of experiments (DoE) or QbD – also add to our understanding of what happens downstream. A good example is a study modeling lysozyme and lectin separation using hydrophobic interaction chromatography, where the authors developed mathematical formulae to predict displacement and gradient protein separation behavior (4). Molecular properties and interactions may also be used to design process development strategies. For example, the molecular weight, isoelectic point (pI) and hydrophobicity of proteins can all be used to model retention times of a protein mixture in ion-exchange chromatography, making the behavior of the product more predictable (5).

Resin technology and automation

Improvements are continuously made in packed bed chromatography resins to increase efficiency and output, including improvements in binding capacity and increased flow rates, as touted by various resin manufacturers. Alternative approaches to standard reverse-phase, ion-exchange, or size-exclusion chromatography are also being explored, including simulated moving bed chromatography (SMB). SMB has been available for over a decade, but is increasingly gaining favor for its increased productivity, reduced footprint, the ability to recycle buffers, and possible automation. A recent publication used SMB to refold and purify recombinant protein in a continuous process, demonstrating up to 60-fold higher throughput, 180-fold higher productivity and 28-fold lower buffer consumption, in comparison to a

"We have looked at various ways to speed up chromatography, but what if we could bypass it altogether and replace it with something else?"

linear batch process (6). SMB is not well equipped to separate complex mixtures, but adding more zones to SMB via multi-column solvent gradient purification continuous processing (MCSGP) adds the capability. MCSGP is a developing technology has been shown to increase purification productivity and yield, but the conditions are often not optimized. Several groups are exploring ways to model and control separation performance in an effort to optimize and automate a process that would meet the requirements for both productivity and product purity specifications (7,8).

On a lab or clinical scale, exciting new technologies like automated robocolumns can be used for high-throughput process development, which can help relieve bottlenecks by reducing process development time at the drug candidate stage or cutting labor costs. For example, a study was completed demonstrating successful comparability of small-scale automated robocolumn processing with large-scale processing with a variety of resins (9).

Throwaway chromatography

Single-use or disposable plastic equipment may offer greater flexibility and efficiency than traditional steel and glass systems, but disposable chromatography equipment has yet to take off in a big way, largely due to high resin costs. High-binding and high-capacity resins, which achieve the most efficient and pure separations, come at a high cost, and many biologic manufacturers are looking to increase the ability to recycle resins rather than dispose of them. Others are using the resin a few times, rather than "single use." Despite this, the market for disposable packed beds is growing, with up to a 15 percent increase expected in 2014 (10).

Anything but chromatography

We have looked at various ways to speed up chromatography, but what if we could bypass it altogether and replace it with something else? This concept – sometimes referred to as 'anything but chromatography' (ABC) – is an attractive one for companies. Various alternative separation methods have been proposed, including precipitation and high-performance tangential flow filtration (11). Another replacement separation technique, aqueous two-phase partitioning, uses two mostly water-based phases, which contain, for example, a polymer (e.g., PEG) or a salt (e.g., phosphate) to separate an antibody by "salting out" (12). Two-phase partitioning has the potential to reduce cost, increase capacity and overcome the limitations of diffusion that can occur in chromatography.

These are just some of the developments that are opening up the downstream processing bottleneck. With the regulatory emphasis on QbD and the economic imperative to do more with less, it's clear that we will need further research and development – and some creative thinking. I'd like to end by handing the baton over to you: what's your solution?

Jaime Marach is a Senior Scientist with extensive experience in synthesis and downstream processing of large peptides, and the development and validation of analytical methods.

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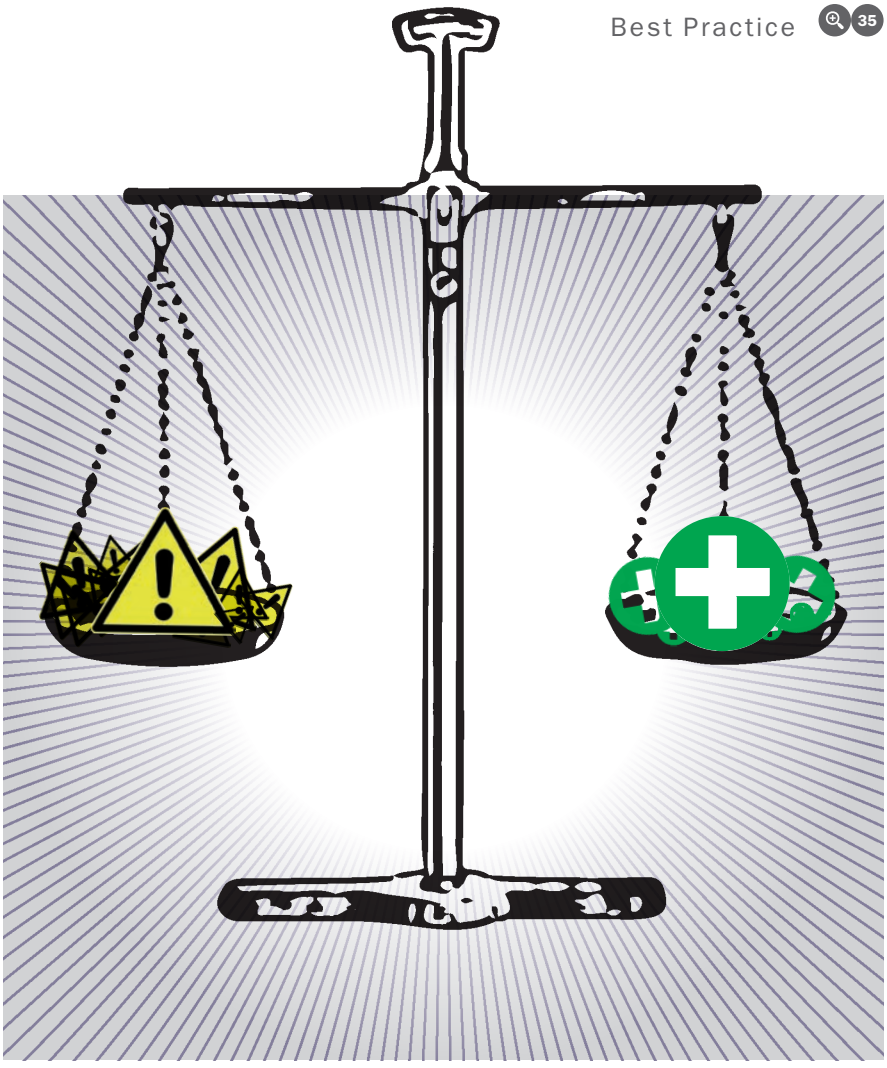
Safety First - Sizing Up Biologics Side Effects



Biologic medicines present unique challenges for pharmacovigilance. And with biosimilars hitting the market, life just got more complicated – especially when products share the same name.

By Catherine Akers

It is widely acknowledged that full reporting of all adverse drug reactions (ADRs) is unlikely; however, the information that we do gather through pharmacovigilance (PV) is crucial for timely remedial action. Here, I give an overview of the unique challenges faced by PV systems when considering biologics and shed light on how a simple change in prescribing practices could help improve traceability – one of the key factors in ensuring accurate PV.

Biologics are complex to develop and manufacture, and the resulting product has a molecular structure and weight that is much larger than traditional 'small-molecule' products. Recent publications have also drawn attention to "non-biological complex drugs" (1), which may share some challenges with biological medicines, but these are outside of the scope of this article.

Benefit vs risk

Biologics are a mainstay in modern medicine but, as with their small-molecule counterparts, they can cause ADRs. At the end of development, a biologic's known safety profile is based on data from clinical trials of limited duration and size; although there may also be known therapeutic class safety risks identified with functionally related biologics. As many of these products are developed for chronic administration it is important that the safety effects of the product continue to be collected in the post-authorization setting through PV. Biologics can be associated with specific ADRs, caused by a number of key factors (2).

Unique properties

Size

The large molecular size of biologics means that they can be 'seen' by the body's immune system, which is in direct contrast to small-molecule products, which enter the body unnoticed. The immune response to the larger biological molecule results in the production of antidrug antibodies (immunogenicity).

""As many of these products are developed for chronic administration it is important that the safety effects of the product continue to be collected in the post-authorization setting."

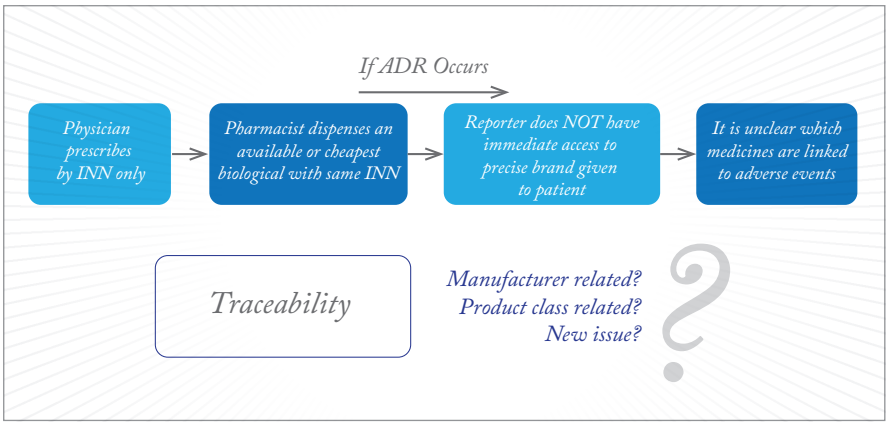


Figure 1. ADR reporting with INN prescribing.

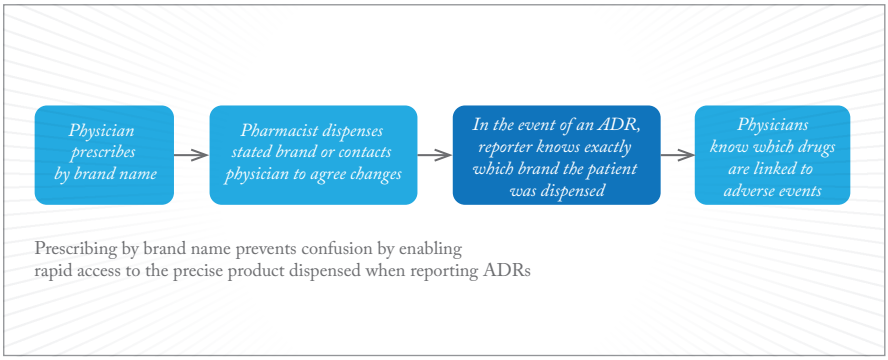


Figure 2. ADR reporting with brand name prescribing.

Immunogenicity may have no clinically relevant impact on safety or efficacy, or it could be associated with ADRs. The severity of such immunogenicity-mediated ADRs can range from very minor; for example, swelling or redness at the injection site, to life-threatening conditions, such as pure red cell aplasia – a very rare immune reaction seen in patients administered with recombinant epoetin (3), or thrombocytopenia, which can be seen in patients administered with recombinant thrombopoietin (4). In both examples, patients develop antidrug antibodies that bind to both the recombinant protein and the body's own endogenous supply, rendering both inactive and leading to loss of function with serious safety implications. It should be noted that such instances are rare (3,4).

Immunogenicity often occurs weeks or even months after the first administration. Therefore, it is important that PV systems are able to detect signals when they occur and accurately attribute them to the causative agent, both for the clinical benefit of the patient, and to determine if factors such as variations in manufacturing were responsible, so that preventative action can be taken (5).

Manufacturing

Biological medicinal products require complex manufacturing processes that involve many individual steps and hundreds of in-process controls (6). As the products are manufactured in living systems, the final medicines have batch-to-batch variability, are relatively unstable and, consequently, display a dynamic safety profile (6).

Manufacturing changes are also common during the lifecycle of any product and may occur for a range of reasons, including compliance with regional requirements, a new manufacturing site, or supplier changes. Such changes may affect the safety profile of the medicine – and there are notable examples in the public record of this – although in most instances there are no problems (7-9). Of course, changes are always assessed for their effect on the safety profile of the medicine and appropriate testing is conducted, but we can only know for sure that there have been no adverse effects on safety once the product is being used in practice.

Inaccurate pre-clinical models

The pre-clinical models used in standard development do not always give a good indication of how the biologic will react in a human. Biologic medicines are engineered specifically to interact with human biological targets and the effects in animal models may not directly reflect the same biology anticipated in humans. The potential consequences were demonstrated with TeGenero in 2006, when pre-clinical models failed to predict a cytokine storm when the product was administered to human volunteers (10).

And if that wasn't enough...

In recent years there has been a fourth consideration when discussing safety of biological medicinal products: biosimilars. Biosimilars are designed to mirror a biological medicine already on the market (once the originator's product patent has expired) (11), but because manufacturing details remain confidential even after patent expiry the biosimilar is produced via a novel manufacturing process, with the same risk of batch-to-batch variability and susceptibility to profile changes described

above. In terms of PV, we need to consider biosimilars as separate products.

What's INN a name?

Once a healthcare professional or patient becomes aware of a side effect they are responsible for reporting it to the national regulatory authority and/or the manufacturer (12,13). In a situation where there is a single product with a unique name or where two or more identical products share the same name (such as small-molecule generics), the name of the product on the report will always allow the side effect to be attributed accurately so that any necessary remedial action can be taken, such as adding new warnings in the product labeling or removing the product from the marketplace.

As an example, let's look at the number of reports from the public information available in ADR reports in EudraVigilance for Humira® (adalimumab). As of September 2014, 28,211 events have been reported (14). Although no timeframe is given for the reporting period, if we consider that the product was first registered in 2003, we can estimate that around 2500 reports are received each year. In this case, we can be sure that all events have been ascribed accurately, as there is only a single product.

However, there is precedence for biosimilars to share the same International Non-Proprietary Name (INN) as the reference product because of their similar nature (15). Let's consider a biosimilar version of adalimumab. The two biological medicinal products (reference product and biosimilar) could share the same INN. Now, let's imagine that after authorization the biosimilar displays a previously unseen ADR. A PV report where only the INN is provided would not allow the side effect to be attributed to a single product, but rather to both the reference product and the biosimilar. Therefore, the signal may be misguided and could delay preventative or remedial action, which is illustrated in Figure 1 (16). However, by encouraging physicians to use the brand or trade name when prescribing biologics, the issue can easily be avoided (see Figure 2) (16).

"By encouraging physicians to use the brand or trade name when prescribing biologics, the issue can easily be avoided."

The naming issue was identified by the UK's Medicines and Healthcare products Regulatory Agency (MHRA), which issued a statement in 2008 in their Safety Update that instructed physicians to prescribe biological medicinal products by brand name (17):

"To allow us to perform product/brand-specific pharmacovigilance, when reporting a suspected ADR to a biological medicine (such as blood products, antibodies and advanced therapies [such as gene and tissue therapy]) or vaccine, in addition to the substance please ensure that you provide the brand name (or product licence number and manufacturer), and the specific batch-number, on the report."

The European Union (EU), which has led the way in biosimilar development, recently acknowledged the unique safety profile of biosimilars in its so-called PV legislation (18,19). The legislation, which came into effect in July 2012, specifically calls out the need for all ADRs involving biological medicinal products to be reported by trade name rather than INN. In Europe, all medicines must have a trade name that is either an invented brand name or a combination of the INN and the registered sponsor's name (e.g., Filgrastim Hexal®), which allows safety profiles to be ascribed accurately and ensures that action can be taken on a product-by-product basis. As European Member States have been implementing this requirement, it is interesting to note that the MHRA has amended its electronic Yellow Card scheme (which is used for submitting ADRs to the agency) to request the specific brand name of the biological medicinal product. The MHRA has also been proactive in providing guidance to prescribers to provide the brand name to prevent any uncertainty when reporting ADRs (20).

A global solution?

Other regulatory authorities outside of Europe may not be able to apply the trade-name approach or may also seek a distinguishable, non-proprietary identifier for independently manufactured biologics. Bearing this in mind, the INN Expert Group recently recommended that the World Health Organization – which is responsible for issuing INNs – develop a system for assigning biological qualifiers (BQ), an alphabetic code assigned at random to a biological active substance manufactured at a specified site (21). The BQ would be used in combination with the INN to provide a unique reference for the manufacturer and the manufacturing site. This proposal continues to be discussed by the Expert Committee, but I believe that it would be of great use in terms of PV and supporting traceability. Additionally, if this system were to be adopted on a worldwide basis, it would be possible for ADRs reported for biologics to be easily communicated to all regions, enhancing

"We're likely to see more discussion ahead of a solution, but whatever path is chosen, efforts must be made to ensure that any requirements are properly understood and implemented."

global ADR signaling initiatives.

However, although the main concept is sound, industry groups, such as the International Federation of Pharmaceutical and Manufacturing Associations, are concerned by some aspects; for example, the linkage of the BQ with the manufacturing site, which could result in unnecessary BQs being generated for the same product, if it is manufactured at multiple sites. It could all get very confusing for prescribers and patients (22).

We're likely to see more discussion ahead of a solution, but whatever path is chosen, efforts must be made to ensure that any requirements are properly understood and implemented. What is clear is that all stakeholders (prescribers, patients, the pharmaceutical industry, governments) have their part to play in ensuring that PV systems contain accurate information to ensure that safety signals are collected post-approval – and then analyzed without delay.

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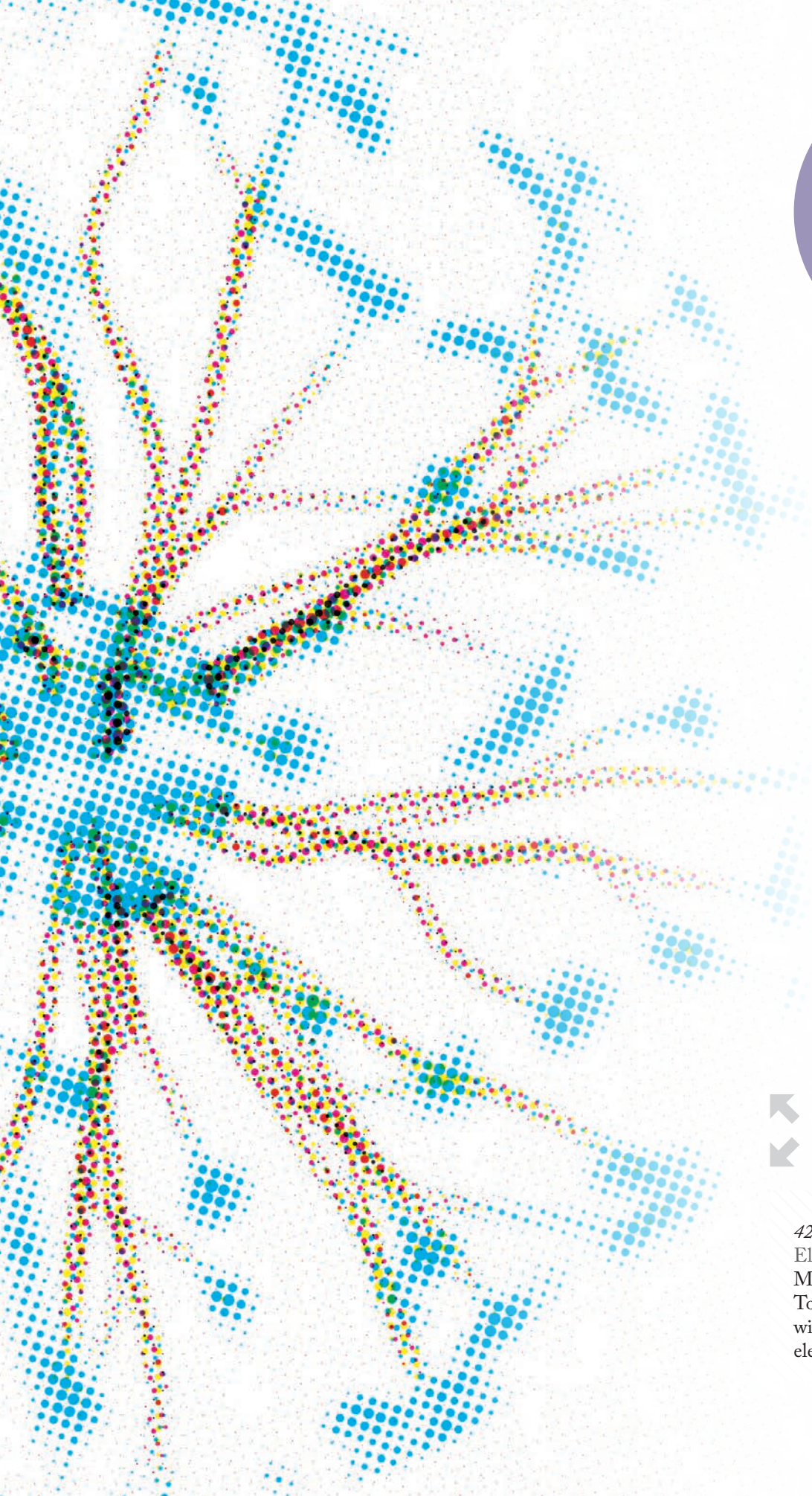

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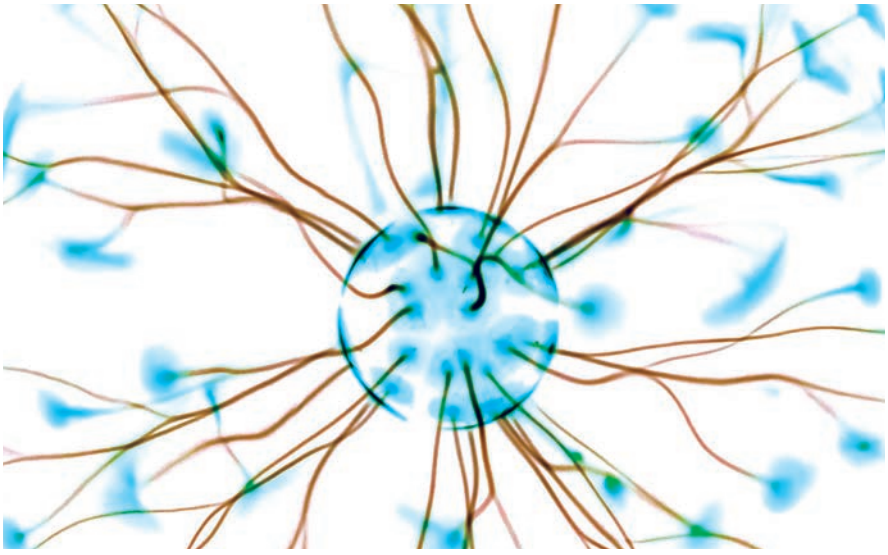
42-44
Electrifying R&D Acceleration
Mark Taylor and Susana Da Silva Torres share their experiences with new applications for electrochemistry in pharma R&D.

Electrifying R&D Acceleration



Electrochemical reaction cells are finding new applications in the pharma R&D lab that could offer big time and cost savings. Here, we share our experiences using electrochemistry with on-line mass spectrometry to study pharmaceutical stability and oxidation products – and explain why we're electrochemistry converts.

By Mark R. Taylor and Susana Da Silva Torres

Electrochemical reaction cells have been used in analytical chemistry for over 50 years (1). Exploiting nature's redox reactions of organic species, these systems have enabled us to achieve selective and sensitive detection in chromatography (2) as well as benchmarking stability of products susceptible to oxidative degradation (3). However, until recently, the use of electrochemistry as a method of producing redox products for further study has not been routinely applied in the majority of pharmaceutical R&D laboratories.

The pioneering work of Professor Uwe Karst and his co-workers at the University of Münster has shown that commercial lab-scale electrochemical reaction cells (in our case a Roxy Potentiostat system from Antec, the Netherlands) can be routinely applied to generate pharmaceutical metabolite profiles very similar to those observed in vivo and in vitro using enzymatic digestion (4). There are obvious advantages to being able to produce metabolites of a drug substance quickly and cleanly in real-time using electrochemistry with on-line mass spectrometry (EC-MS) rather than traditional in vitro methods using expensive xenobiotic metabolizing enzymes or cell digestions, where lengthy sample preparation for MS is often required due to potential interference from the sample matrix. Use of a reaction cell with on-line MS or LC-MS system allows for much more rapid and convenient study of redox metabolites and the EC-MS technique is starting to be applied more widely as a result, giving faster access to key data on metabolite profiles and structure. The oxidized species produced in these reactions are often unstable; by studying them in real-time, we can avoid bias from product decomposition during sample preparation and storage.

Stability testing

As well as in vivo metabolism, oxidation plays a major role in pharmaceutical stability and, along with hydrolysis, is one of the most common mechanisms of drug degradation. Pharmaceutical companies go to great lengths to understand and control these potential degradation mechanisms in their products. Gaining an understanding of the theoretical and real oxidation product profile of each new pharmaceutical product is a regulatory expectation and of fundamental importance to protecting patient safety and ensuring robust and relevant stability indicating methods, to provide a basis for stability studies. Extensive stress testing through forced degradation is routinely applied using a range of in silico and in vitro methods designed to cover all possible routes of potential degradation including thermal, humidity, photo and chemical (hydrolytic and oxidative) stress tests (5).

Just like the metabolic studies we mentioned earlier, electrochemical reaction cells coupled to MS and LC-MS give us a new and convenient way of studying the redox stability of pharmaceutical products. We can now study reactions on-line and in real-time using high-resolution accurate mass MS, which is able to churn out proposed chemical formulae of products in a matter of seconds (6). The use of electrochemical cells obviates the need for lengthy and often hard-to-replicate chemical treatments using caustic reagents, such as hydrogen peroxide. By fine-tuning the applied cell potential we can optimize the process to achieve the maximum yield of specific target reaction products prior to on-line or off-line analysis by complementary spectroscopic techniques, such as nuclear magnetic resonance (NMR) or bioassay (7).

An addictive example

We used EC-MS in direct infusion mode to study naltrexone, a potent narcotic antagonist used in maintenance treatment for opiate and alcohol dependence, which is known to degrade by oxidation (9). Figure 1 shows an overlaid ion intensity plot of a naltrexone standard solution, prepared in a simple ammonium acetate electrolyte buffer, as it is syringe-pumped through an electrochemical reaction cell into a high-resolution mass spectrometer. As the applied cell potential was linearly increased, the intensity of the naltrexone substrate mass ion (m/z = 342.1705) decreased and ion intensities from naltrexone oxidation products increased and decayed as new oxidation products are formed. Mass ions consistent with formation of a dimer (2-2'-bis-naltrexone), dehydrogenated naltrexone and associated dimer (M-2H) and from the addition of one, two and three oxygen atoms (M+16, M+32, M+48) to naltrexone were observed as the oxidation potential was increased. It was interesting to observe the relationship of the different products to applied voltage – you can see the formation and decay of reactive intermediates and products in real-time as voltage was increased. Analysis of the redox cell effluent by LC-MS suggests that isomers of the oxygenated reaction products are formed from different sites of hydroxylation. The results were consistent with what we already know about the drug – species formed at lower potentials are observed in laboratory stability studies and special stabilization agents have been proposed to mitigate against their formation in pharmaceutical products (8). The ability to gather data by EC-MS without the need for specialist reagents and reaction time-course sampling is hugely attractive and gives us a head start to stability-relevant data.

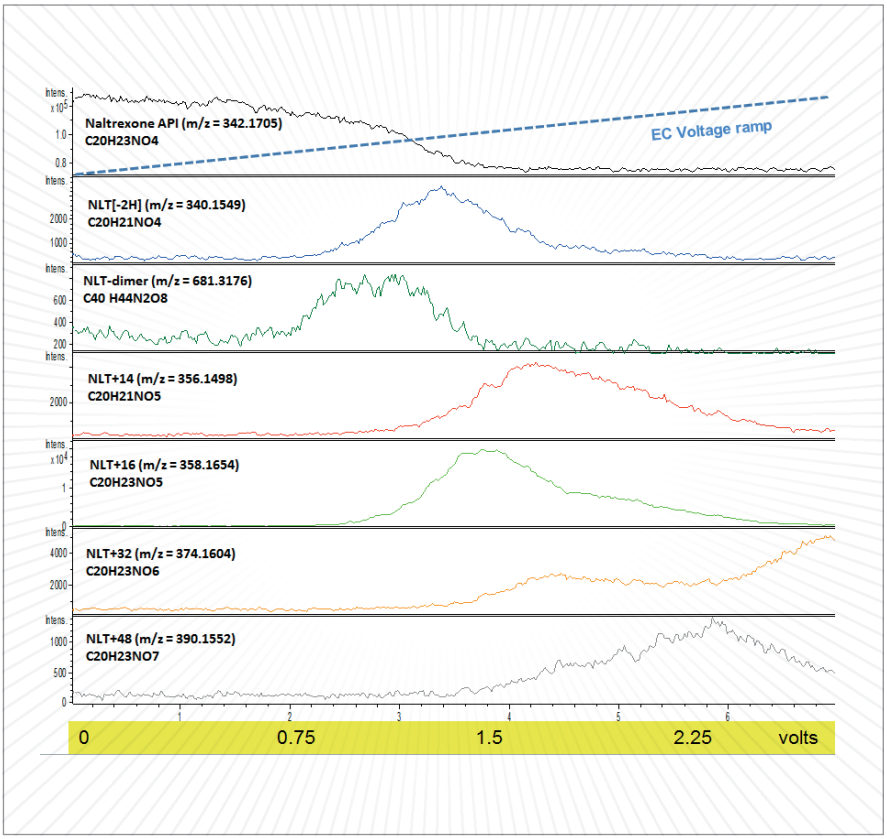


Figure 1. EC-MS ion intensity plots of infused naltrexone and electrochemical cell oxidation products using a magic diamond electrode and applied voltage ramp (0-3V in 7 minutes).

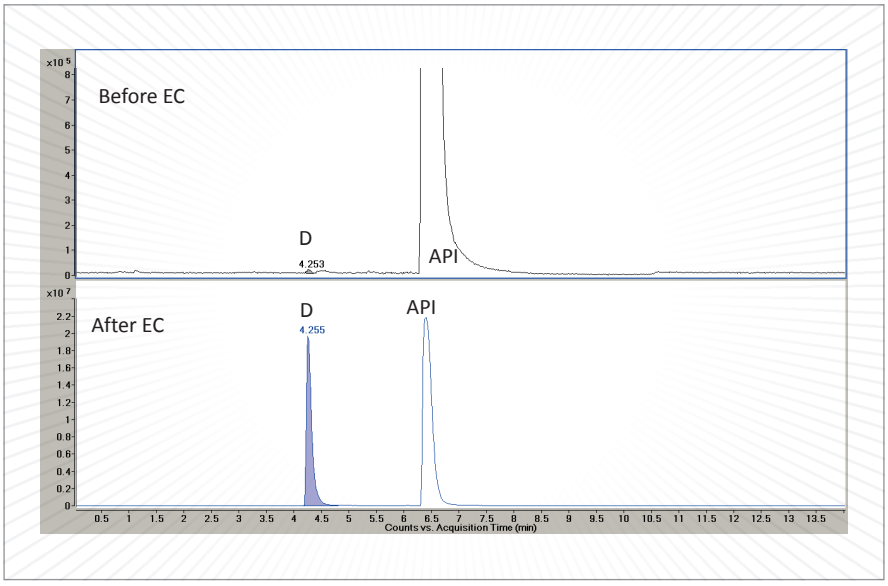


Figure 2. Overlaid LC-MS chromatograms of a pharmaceutical API sample showing enrichment of a trace degradant (D) following electrochemical oxidation (EC).

Amplifying oxidation products

Once pharmaceutical oxidation products

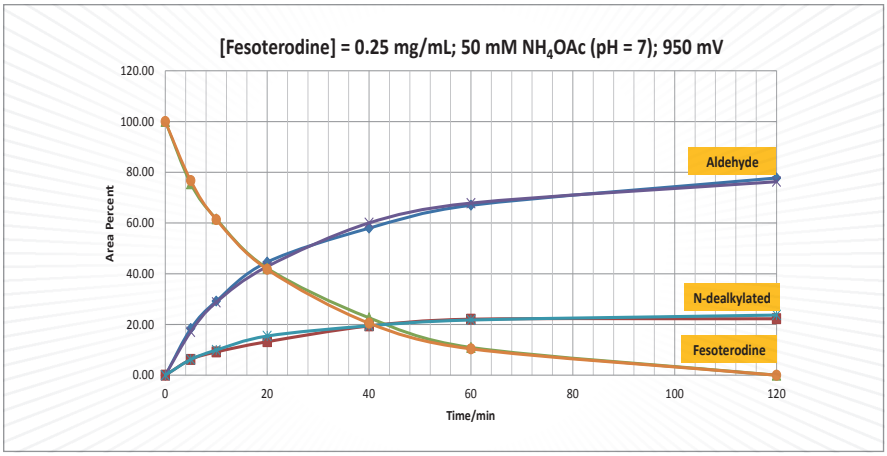


Figure 3. Overlaid curves showing the rate of formation of two target oxidation products produced by electrolysis of 20 mg fesoterodine fumarate (9).

cross a particular concentration threshold relative to the active pharmaceutical ingredient (API), regulators expect their structures to be identified. Markers of the oxidation products are often needed to validate stability indicating methods and to ascertain their relative response factors in the selected quantitative analytical methods. It can be quite a challenge to identify trace (≤ 0.1 percent) levels of oxidation products, as they can easily be drowned out by the relatively large quantities of main-band API. In our laboratories, we have used EC-MS and, more recently, preparative synthetic electrochemistry to accelerate identification of the oxidation products. By electrochemically depleting the amount of API relative to that of the oxidation product it is quite possible (by selecting the optimum cell potential) to increase the concentration of an observed trace oxidation product to 50 percent or more of the total chromatogram peak area in just a few minutes (Figure 2). This provides enough material for more sophisticated LC-MS-MS experiments to be performed and for structure confirmation and concentration measurement using NMR, without having to resort to complex sample preparation techniques.

Making oxidation markers

Synthesizing API oxidation product markers for method development and validation can be technically challenging using traditional wet chemistry approaches, often requiring weeks of chemist time, plus sourcing and evaluation of starting materials and reagents. We wanted to see if we could use an electrochemical synthesis cell to produce oxidation product markers rapidly and directly from solutions of the API dissolved in electrolyte (9). Using fesoterodine as a model compound, we were able to produce the oxidation products directly from the API without the need to source special reagents (Figure 3). Better yet, we observed that the reaction was much more rapid and selective than in-house attempts to produce these oxidation products using traditional approaches. Attempts to produce larger amounts of material (starting with 80 mg substrate) were successful too, with the trade-off that the total conversion rate in two hours was reduced to approximately 75 percent. A mixture of products was produced so individual pure products were recovered using preparative HPLC and centrifugal evaporation.

As early adopters, we approached the use of EC-MS to support pharmaceutical stability and structure elucidation studies with trepidation. We were concerned that the technology would fail to deliver in a high-pressured and busy laboratory. However, in every case, electrochemistry has provided a time and labor cost saving that has easily repaid the capital investment. We are now using the technique routinely to facilitate understanding of pharmaceutical oxidative stability, enable structure elucidation and simplify synthesis of oxidation product markers, and we expect to see more and more laboratories joining us in the years ahead.

Mark R. Taylor is a Senior Analytical Chemist and Susana Da Silva Torres is a Post Doctoral Research Student in Pharmaceutical Sciences, Pfizer Worldwide R&D, Sandwich, UK.

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Our Unholy Alliance
Are science and business tenacious partners in a shaky marriage or eternally bound nonidentical twins?

Our Unholy Alliance

Science and business: tenacious partners in a shaky marriage or eternally bound nonidentical twins?

By Lee DesRosiers

Technology collides with human behavior. That's where the action is – either phenomenon alone is prosaic, which is why biotechnology and its motley relatives are so fascinating and – let's face it – the only game in town. Of course, the ancient art of brewing was the first really useful biotech application in commerce. But since the advent of beer, the business of science has really only accelerated in the last 40 years or so…

A pharmaceutical company, in conjunction with its partners, manipulates large clinical trial data to deliberately mislead the authorities. It's a misguided attempt to gain approval for a drug that cannot succeed – "cooking the books" in accountant vernacular. Directors of institutes in Tokyo and the National Institutes of Health commit suicide in response to one of their staff attempting fraud.

Are these events related? Do commercial concerns and academic goals drive otherwise discerning adults over ethical boundaries? Certainly. But every day, all day, all over the world, scientific and commercial transactions of all kinds occur ethically and fairly (subjective though those terms are). Both the business and scientific communities are remarkably hard on unethical behavior. And rightly so, but let us not pretend that we don't understand the pressures.

Why don't you get a job?

I grew up with biotechnology – that is to say, I grew up as biotechnology grew up. In the late 70s, when biotech started to "work" (showing potential in actual applications), I got a job. I moved from a protracted academic "lifestyle" to employment in the lab. To be more specific, I was hired to further develop a single celled photosynthetic bacterial protein source for developing countries.

It was a morally unassailable position that I didn't hesitate to boast about to my reprobate college friends – all for a whopping $10,500 Canadian a year (twice the "$100 a week" my father would have described as a good salary 15 years earlier). Fifteen years later, in the intoxicating world of senior management in the life sciences, that salary seems like a rounding error…My first "real" job was classic "micro", and a couple of grants later, it would be early "molecular." I was a player (albeit a peripheral one) amongst the fighter jet pilots of biotech: the gene jockeys. This was still in a totally academic environment, of course.

We redistilled our own phenol, worked daily with acrylamide, hydrazine, DFSO, ethidium bromide, P32 and I125. Toxic, carcinogenic, radioactive, corrosive, explosive: all part of the macho arrogance of molecular biology – the only field that mattered back then.

I learned to sequence DNA, to do restriction fragment length polymorphism analysis, to clone DNA in the days when these processes were opaque, inscrutable, finicky, dangerous, involved, and laborious. It was a time when restriction enzymes were still spoken of with awe. And, at maybe 200 bases a day, it would have taken me a tad over 41,000 years to sequence the human genome…We chewed and spat out inscrutable jargon, those who couldn't follow were doomed to be passengers in the future we were creating. We spoke of the elegance of our experiments. We scoffed at immunology, micro, plant biology but especially medicine. Why struggle to save aging overweight humans? It was their own fault and it would never happen to us. We understood aging and mortality but assumed we were exempt. Business might as well have been astrology.

We would ask ourselves: who but the most intellectually challenged – the most lacking in resolve and imagination – would ever consider any type of corporate affiliation? To "prostitute oneself " was the standard analogy. Yes, the impression among us at the time was that business people were amoral, insincere and unintelligent. It was acceptable for a scientist to simply not show up to an agreed upon rendezvous with one of the ubiquitous sales representatives that bravely sought our attention. We pitied them. We mocked them. They didn't warrant our respect. And we were far too intelligent to be sold to.

The sales people we met had been apparently forced, due to a lack of intelligence, to be in the questionable, dark world of business. Mysteriously, we thought our pursuits purer, although there was certainly no mystery about the source of our funding: taxes from the very companies and people who were beneath us.

Isn't it time you moved out?

When biotech "moved out of the house" into commerce in the 80s, I was caught up in the wave and went from being a molecular biology research assistant to a product manager for a biochemical company, selling to the same people I had previously worked with. My excolleagues recoiled in horror.

It turned out to be a subtle, judgmental world – one of shifting loyalties and difficult decisions. Constant dilemmas involved two positive alternatives or two negative alternatives. It was as disorienting as a concussion.

I had to learn to dress. In general, business people know how to dress; academics don't, as it is too banal an issue to consider. I showed up on my first day in brown suede shoes and a blue suit that I had been obliged to purchase for my

father's funeral two years earlier. At the end of that seemingly relentless first day, my boss advised me to "lose the shoes".

Business people (ideally) had emotional intelligence: they looked you in the eye, they shook your hand firmly. Scientists at the time did not make eye contact, if they could avoid it, and were unfamiliar with any physical contact – or so it seemed from their dead fish handshakes.

The affable back-slapping business mentality was sneered at and looked down upon by science people while business people saw scientists as socially inept, stylistically incompetent introverts who lived as perennial school children in clutter and relative poverty, just to avoid the responsibility of adulthood.

This clash of culture became very apparent to me when I returned to the lab, visiting as a product manager with the local sales representative. I was particularly struck by the disorder, squalor and generally unhealthy feel to the lab. And then there was the petty possessiveness; even pens had nametags on them and people were proud to have a phone to call their own.

When I first got the job, my new company called me in my old lab to ask if I preferred the bookcase or the credenza for my office. Office? I was stunned, I didn't even know what a credenza was. And I'm still not entirely sure.

Emotional intelligence, while in short supply everywhere, is required to excel in business but, until more recently, relatively underemphasized in science, where a gruff, irritable reclusive attitude was seen as part of the aura. Intelligence – in its brute direct form – is "nice to have" in business, but essential in science. Business is more about resilience, intestinal fortitude, looking people in the eye, reading the situation, thinking on your feet, actually liking people, having the maturity and the security to let others excel and surpass you. Admittedly, these often turn out to be only partially achievable ideals.

Scientists, despite their occasional bravado, were timid and conservative in their approach. Business required courage and a thick skin. The closest a scientist might come would be during a thesis defense. Scientists thought applying for a grant constituted pressure. The pressure in sales, marketing, management is monumental by comparison – and is in full bloom daily. In graduate school, 65 percent is a pass. In business, 95 percent of forecast can still be a disaster.

"Scientists dreamed of the apparently endless money the naïve business world would lavish on them – money that had been previously allotted unfairly to undeserving corporate drones."

In the intervening decades, science has moved into business and vice versa and these effects have been lessened. There was a brief period when there seemed to be no end to biotech, when an idea was enough to start a company. Scientists dreamed of the apparently endless money the naïve business world would lavish on them – money that had been previously allotted unfairly to undeserving corporate drones.

But we've all grown considerably since then. Realistic, achievable collaborations too numerous to mention have been successful. There has consequently been considerable cross pollination: business 'models' cannot seem to stop trying to apply scientific models to business scenarios and fields like pharmacoeconomics have bloomed. More and more often it is the science of business and the business of science.

Academic approaches to business and commercial mentalities in science notwithstanding, the drive to bring purer applicable research into medical, diagnostic and biotech carries its own limitation.

A commercial concern will acquire a research effort or a researcher, instantly removing them from the market the business is most interested in and inundating them with the very corporate culture the company is trying to enlighten. Small start-ups with aggressive, innovative approaches are swallowed by large Pharma who are looking to get closer to the real market. The corporate culture is methodically forced downward until the academic connections and approach fade under a results driven regime.

Is this on the test, professor?

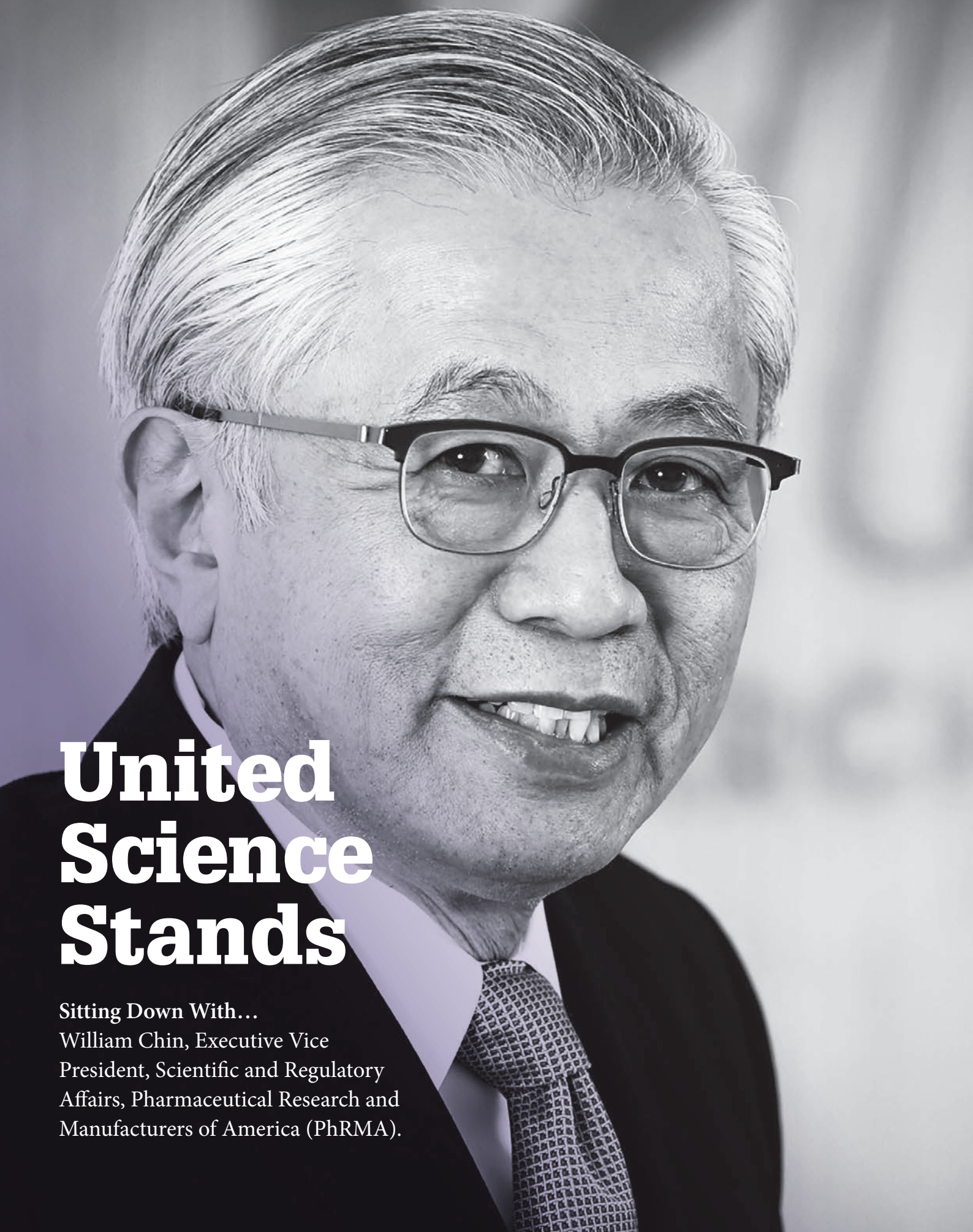
But all is not lost. The marriage of business and science changes color and texture. Progress continues. Wounds heal.

Now, I teach management (management "science", actually) to young graduate students, many of them in high-tech or medical fields. I try to broaden their view and strengthen their hold on the future. The young talent drawn to business and science are no longer so clearly delineated. They display an admirable open mindedness; they want to know both worlds as one.

Big money doesn't necessarily ruin everything – and science is big money now. It might yet be the biggest. The two worlds alike will always be driven by the same hopelessly addictive allure. Promise.

Besides, we will always have beer.

Lee DesRosiers is a lecturer at McGill University in Montreal, Canada.



United Science Stands

Sitting Down With…
William Chin, Executive Vice President, Scientific and Regulatory Affairs, Pharmaceutical Research and Manufacturers of America (PhRMA).

You moved from academia to pharma quite late in your career – why?

When I moved to Eli Lilly, a lot of people thought I'd gone crazy. I was in academia for 25 years as a physician–scientist and was a Professor at Harvard. But during the latter part of my academic career I got more and more interested in translational research and the whole issue of how we can better move ideas from the bench to the clinic. In many ways, industry was setting the pace back then – and I wanted to be part of it. It was a steep learning curve and at times I felt like I was starting out again as a new Fellow – it was disquieting but also energizing.

What attracted you to your current role at PhRMA?

After 11 years at Eli Lilly, I returned to Boston to become the Executive Dean for Research at Harvard Medical School. There, my job was to foster work in translational science and work on creating better collaborative research partnerships, primarily between academia and industry. But it was hard to get companies to come together. So when an opportunity came up at PhRMA to lead scientific and regulatory affairs and to bring scientists together from industry and academia, I found that particularly exciting.

Tell us more about the collaborative partnerships.

Companies are by nature competitive in a business sense. There is a tendency to think that the science in the companies must be competitive too – but that's not necessarily true. What if we didn't need to keep repeating the same work? If we could share our findings, it could be a tide that raises all boats. Groups could come together to share information and use that work as a platform to develop competitive products. In February there was a great example of precompetitive collaboration, coordinated by the National Institutes of Health – the Accelerating Medicines Partnership. The concept was to bring together biopharmaceutical companies, academia and governments to work on some of our biggest medical problems, including Alzheimer's disease, Type 2 diabetes and autoimmune diseases. For instance, we know precious little about Alzheimer's disease – we don't know what causes it or what leads to some patients having faster progression than others. One company alone is unlikely to ever find these answers, but by pooling their resources and talent, multiple companies stand a chance.

How do you expect to see these collaborations develop in the future?

While there are certainly plenty of precompetitive partnerships out there, I would argue that they are not all equally effective. The challenge for the future is to create focused partnerships that provide results that meet the needs of all partners. It's very important to make sure there is an alignment of goals. Otherwise, the project will probably stall and everyone will be left disappointed. We need to look toward those who are succeeding, learn from them, and apply that knowledge to new collaborations.

What developments will be the game changers of the future?

I'm very excited about progress in cancer therapies. We now know many of the molecular targets that lead to cancer and we're developing medicines that attack those targets. Cancer is not just one disease – there are hundreds of permutations – and our increasing knowledge is allowing us to target the therapy to an individual patient's disease.

Another exciting area is autoimmune disease. For many years, this whole area of immunology was befuddling. We really didn't have a clear picture of how the system works – how it protects us and how it harms us when it goes out of control. As research advances, we now have hope that we might make as much progress in this area as we have in cancer.

"If we could share our findings, it could be a tide that raises all boats".

A final example is what we are now learning about the human microbiome. We always knew we had bacteria growing in our guts and elsewhere in our bodies, but somehow no one ever thought that might be important. As it turns out, the bacteria are not just passive residents - they interact with us, talking to our bodies and influencing our health. That has interesting implications for therapeutics.

What is PhRMA's role in moving science – and the industry – forward?

If we can make these precompetitive collaborative partnerships work better, I think they will be key to speeding up progress. Another area of interest is clinical trials, where the system is under pressure due to the low level of participation of patients in such studies. How can we help people to understand that participating in clinical trials is important? We need to help educate people that while it may not help them directly, it is certainly critical for future generations.

You have achieved a lot during your career. What drives you?

That's easy – patients. I'm an endocrinologist by trade and I know how badly patients need better treatments, so the thing that gets me out of bed in the morning is the opportunity to get more effective medicine to patients, more efficiently. And the pharma industry is a big part of the system that allows us to do that.

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