JUNE 2016 # 20

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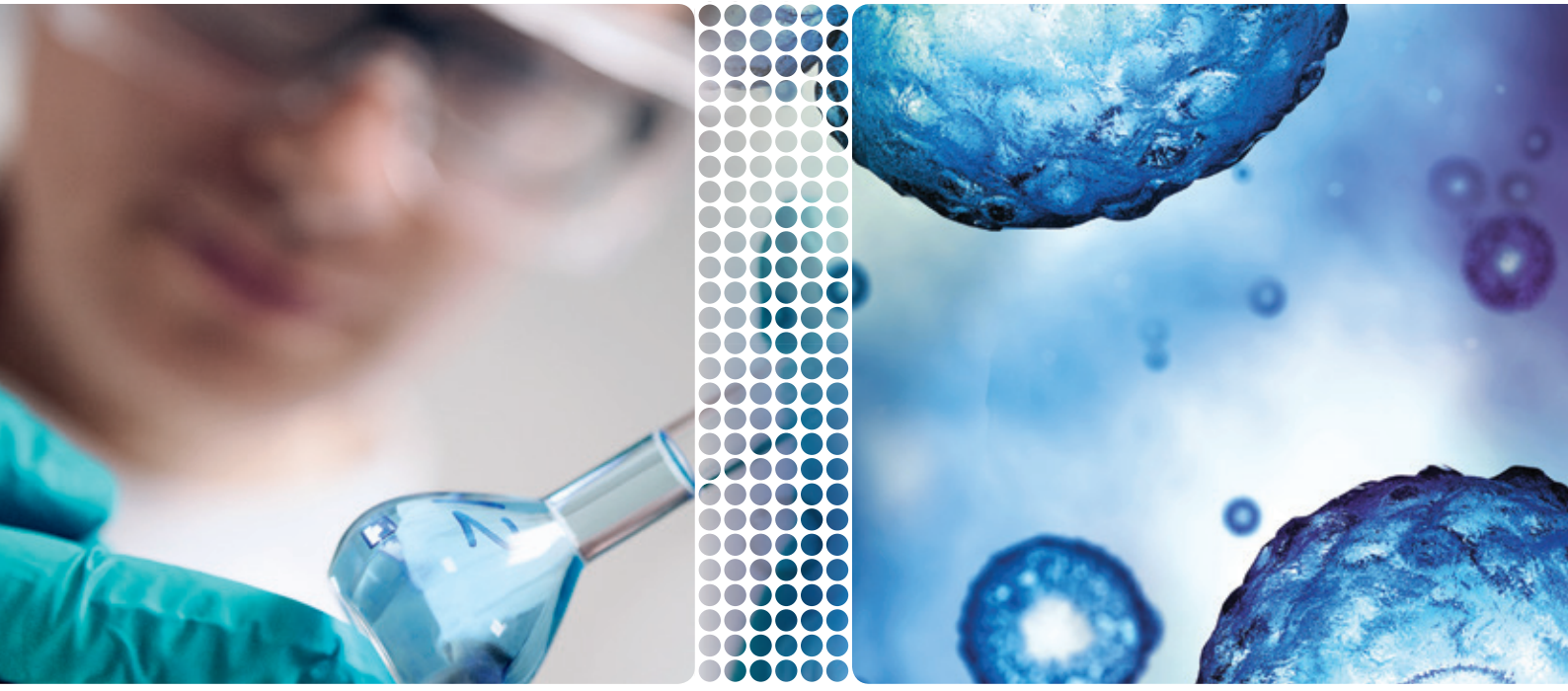

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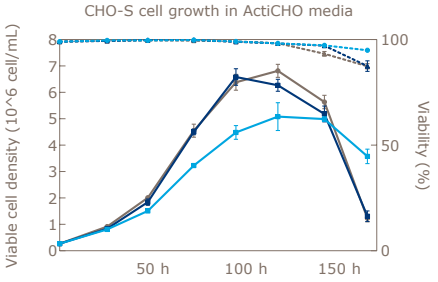

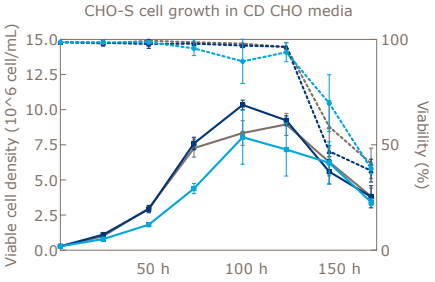

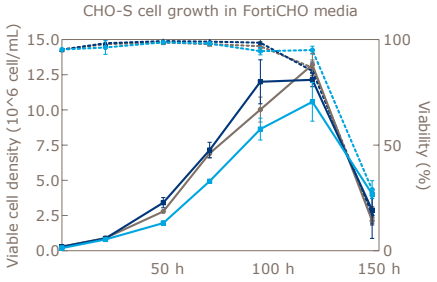

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Online this Month

The Result of The Great British Debate

By the time you receive this issue, the votes in the UK's referendum on whether the country remains a member of the European Union or not will have been counted (and no doubt widely publicized in the media). We examined some of the potential consequences that Brexit may have for the pharma industry in our May issue (http://bit.ly/1Rcrp8I), but for an update of the referendum results and more speculation about the impact, read our online article.

http://tmm.txp.to/0616/Strachan

An Irish Tale of Biopharma

Ireland is a popular destination for investment from international biopharma companies and, according to Barry Heavey from IDA (Ireland's investment agency), the reasons for this are clear: the country's strong track record of compliance and project management, low corporation tax and initiatives to help foster biopharma talent. As part of its mission to help develop the biopharma industry, a National Institute for Bioprocessing Research and Training (NIBRT) was opened in Dublin in 2011. We find out more about NIBRT in this month's cover feature on page 20. But you can learn about the Ireland's biopharma industry as a whole online.

http://tmm.txp.to/0616/Heavey

It's Just a Game

Avid readers of The Medicine Maker will know we've been following the development and launch of 'Big Pharma' – a video game that puts players in charge of their own pharma manufacturing company. The game launched in November 2015 and has since sold 100,000 copies. Find out about the game's newest development online.

http://tmm.txp.to/0616/Wicksteed

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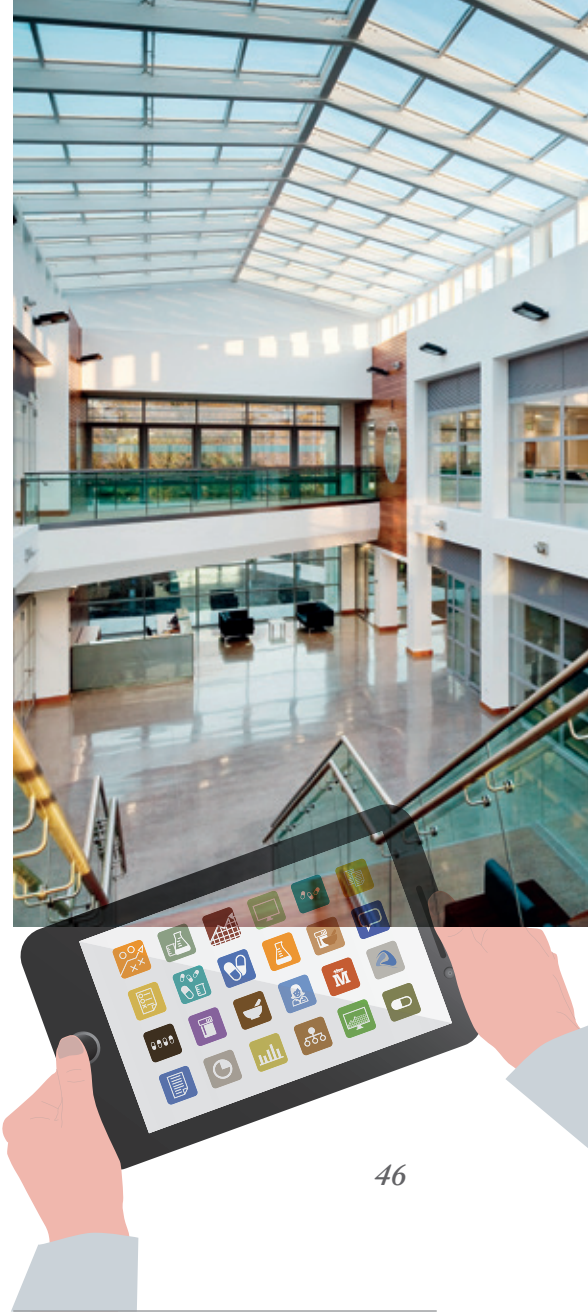

On The Cover

Learning the ways of biopharma at Ireland's National Institute for Bioprocess Research and Training.

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Sitting Down With

the **Medicine Maker**

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The Ups and Downs of Medicine's Vanguard

Cell therapy successes are widely hailed as breakthroughs, but will adverse effects and patient deaths hold the field back?

"Progress is slow in the pharma industry," people say. But I think it's unfair to apply this statement to every aspect of drug development. For example, many of today's medicines are incredible when compared with what was available only 10 years ago. I started writing about drug development when biopharma was in its infancy, and it's been fascinating to watch the field evolve to dominate company pipelines today. But biopharmaceuticals are not the final frontier of medicine. In recent years, another therapy type has been stealing the spotlight: cell therapies.

Today – even though only a few therapies have been approved – news concerning cell therapies is everywhere. In June, for example, results from a stem cell therapy trial for multiple sclerosis in Canada were published showing that most patients saw a substantial improvement in their condition (1). But cell therapies are not without risks – the treatment used for the trial was aggressive and one patient died from complications related to the cell transplant.

The potential of chimeric antigen receptor T-cell (CAR-T) therapies for treating cancer, particularly acute lymphoblastic leukemia (ALL), have received a great deal of attention of late. Also in June, Juno Therapeutics stated that clinical trials of its CAR-T treatment for ALL showed a complete response in 23 out of 30 patients with morphologic disease (2). Novartis has also been running trials for its own CAR-T therapy for ALL – claiming 93 percent remission in pediatric patients (3). However, as with the trial in Canada, Juno and Novartis' trials have not been without complications. Some patients in Novartis' trial experienced cytokine release syndrome and there have been deaths in other trials involving Juno's CAR-T cells.

A patient death in a clinical trial should never be trivialized and it's clear that there is still much to do before cell therapies enter mainstream medicine; however, given that the trials so far have mainly focused on diseases without current effective treatments (beyond medicines managing symptoms), the big question is: do the benefits outweigh the risks?

Regulators, including the FDA, are considering how to monitor the safety of CAR-T therapies (4), and companies are working on how to manufacture cell therapies on a larger scale. The industry seems confident that these therapies can safely make it to patients (eventually), but will they ever be first-in-line treatments? The fact that high percentages of participants in the trials are seeing improvements is certainly significant, but how will the risk-benefit ratio translate to larger patient groups?

Stephanie Sutton
Editor

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Upfront

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

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

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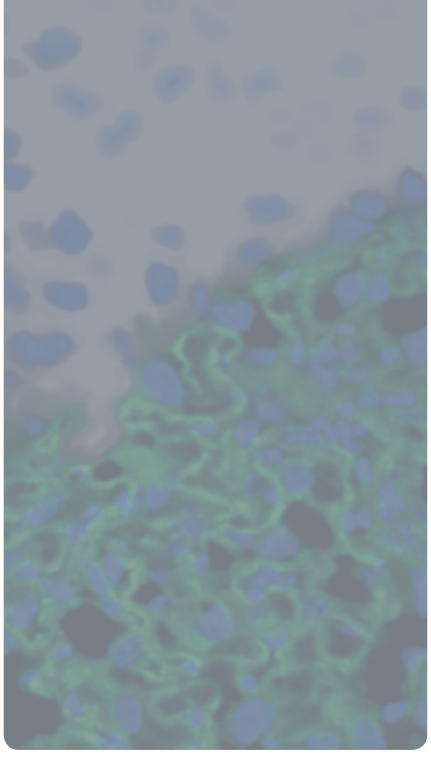

Lynda Harris, University of Manchester

Placental Payloads

Tumor cells and phages inspire a new drug delivery method targeting the placenta

More than 10 percent of pregnant women develop serious complications such as preeclampsia (PE) and fetal growth restriction (FGR), both of which are caused by a poorly functioning placenta. Though a number of potential therapeutics have been identified that enhance placental growth and function in animal models, there are no drugs that can be used to treat PE or FGR. Instead, doctors have to induce early delivery, which puts the infant at increased risk of cerebral palsy in the short term and heart disease and diabetes later in life. Part of the problem is that pregnant women and developing fetuses are particularly vulnerable to drug side effects – making them a high-risk, low-return cohort for pharma companies.

To address this, an international group of researchers have developed a method to safely deliver drugs directly to the placenta (1). The inspiration for the research? Parallels with cancer biology, and a visit from a colleague. We spoke with Erkki Ruoslahti, co-author of the study, and Distinguished Professor at Sanford Burnham Prebys Medical Discovery Institute in La Jolla, California, and the University of California, Santa Barbara, to find out more.

How did you become interested in this area?

From the outset, I was interested in tumor cells. My interest in the mechanisms of metastasis led me to hypothesize that the reason tumor cells metastasize into certain tissues is because they have a specific affinity for the blood vessels of that tissue. The corollary of this hypothesis was that the blood vessels of different tissues would have to be different at the molecular level. That is what we set out to study more than 20 years ago, and we are still working on it today, although we now focus on the vessels of diseased, rather than normal, tissues.

We realized that we could probe the vasculature of different tissues by injecting libraries of a billion or so peptides – expressed on a bacteriophage – into mice. We could then rescue the phage that had ended up in the tissue we were interested in. By repeating the process a few times, we could select for phages with a specific affinity for the target tissue – its blood vessels in particular.

The phage screening could also be used to probe disease-specific vascular changes – and we have identified a number of new tumor vessel markers in this manner (and used the peptides to deliver anti-cancer drugs). We have also targeted wounds, atherosclerotic plaques, inflammatory lesions and, recently, the placenta.

What inspired you to apply the technique to the placenta?

We had not considered using phage screening to target the placenta until Lynda Harris, Lecturer in Pharmaceutics at the University of Manchester, UK, paid us a visit and suggested it. Given the many similarities between the placenta and tumors – they both grow very fast and invade – it wasn't a big step to think that our tumor-homing peptides could also home in on the placenta. In many ways, the placenta is like a malignant tumor under control. Lynda proposed doing a sabbatical in my laboratory to use our technology to target the placenta; and in our recent study, we showed that some of those peptides work very well in placental targeting (1).

What were the main findings?

We used targeted liposomes to deliver cargoes of carboxyfluorescein and

insulin-like growth factor 2 to the mouse placenta; the latter significantly increased mean placental weight when administered to healthy animals and significantly improved fetal weight distribution in a well-characterized model of fetal growth restriction.

What are the challenges of delivering drugs to the placenta?

The placenta is readily accessible from circulation, so there is no problem in that regard. The challenge, however, is that you have to be very careful because the pregnant mother and the fetus are so vulnerable – thalidomide, and lately the Zika virus, are terrible illustrators of that. Only one drug for use during pregnancy has been licensed in the last 20 years.

What are the next steps?

We have, in no way, exhausted the potential of phage screening and peptide targeting in the pregnancy field. It may be possible to find peptides that are more effective and have a more restricted specificity than the tumor-homing peptides we have used so far. For example, targeting specific parts of the placenta may be possible – and I believe Lynda is currently working on that.

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Is Forecasting Futile?

A survey-based report highlights wildly inaccurate drug demand projections

Overestimate demand for your new drug and you could spend millions on a plant that's grossly underutilized; underestimate, and your lack of inventory could result in delays and lost sales. Demand forecasting is crucial when it comes to making good manufacturing decisions. Given all that's at stake, how effective are pharma companies at forecasting demand for new products? Well, according to a survey from ORC International: not very effective at all (1).

Drug forecasts combine scientific, clinical, regulatory and commercial data, but conversion of that data into useful information is difficult. In a survey of 50 pharma industry senior managers, researchers found that over 60 percent of drugs forecasted are either over or underestimated by more than 40 percent – and a substantial number of companies are overestimating peak revenues by 160 percent or more. Nearly all survey respondents claimed that unused or underutilized facilities existed in their network, although underutilization was generally below 25 percent.

Why? According to the report, overestimated demand was typically caused by unexpected market volatility or simple optimism. In the case of underestimation, lack of background data to support forecasting information was usual suspect.

"Demand forecasting is hard because companies need to start pursuing capacity for manufacturing a new drug 3 or 4 years before it is actually needed," says Joe Principe, Vice President of Strategic Partnerships at Patheon, who sponsored the study. "There's no crystal ball good enough to understand the future and companies, understandably, can get it wrong. It's not really their fault – most are using forecasting models to the best of their abilities."

The survey found that many companies react to the problem by investing more in forecasting tools or by outsourcing, as opposed to building in-house capacity based on potentially incorrect demand forecasts. Is there a better way?

According to the report, around 400 new products are likely to be launched in the next three years – 60 percent of which will require unique manufacturing processes. Increased complexity coupled with inaccurate demand forecasts sounds like a potentially bad headache. And if forecasts cannot be improved, coping more efficiently with demand variability is the only pill to swallow. Flexible manufacturing options exist that could mitigate the need to build a new plant – so do these uncertain times represent a tipping point for their uptake? *JS*

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Clinical Trials in Safety Spotlight

The EMA says it will review its standards for first-in-human trials

In January of this year, one man lost his life and 5 others were hospitalized after taking the experimental drug Bia 10-2474 during a Phase I clinical trial in Rennes, France. Since the tragedy took place, two in-depth investigations have been carried out: one by the Temporary Specialist Scientific Committee (TSSC) set up by the French medicines agency (1), and the other by the Inspection Générale des Affaires Sociales (IGAS), the inspectorate for social affairs in France (2). In light of the findings, the European Medicines Agency has initiated a review of its guidelines for first-in-human clinical trials – with the aim of better ensuring the safety of human volunteers (3).

The IGAS report concluded that Biotrial (the French contract-research organization who conducted the trial) and Bial (the Portuguese pharmaceutical company who sponsored it) are partly responsible for what happened based on the dose they chose to administer and the time they took to alert the authorities and other trial participants. The TSSC report concluded that the accident was related to the molecule tested, and that Bial and Biotrial both acted within the current rules, but followed a "flawed testing protocol". The report was very critical of Bial's Investigator Brochure, which "contains many mistakes, inaccuracies, figure inversions… making understanding difficult in several aspects." The authors describe their findings as "highly surprising given the regulatory importance of this document." Though the authors did not comment on whether or not the trial should have been authorized, they pointed out that "of the 63 pages of the Investigator Brochure summarizing the preclinical data, fewer than two discuss demonstration of pharmacological activity for the apparently planned indication." According to the authors, this meant that it wasn't possible to determine an effective dose before "never risk-free" preclinical and clinical development took place. The report also revealed that preclinical tests indicated that BIA 10-2474 had a lower efficacy than the comparator product – a fact that was deleted from the Investigator Brochure. The authors also said they were "astonished" that volunteer selections did not include a neurophysiological assessment.

The EMA says it will take the findings of both reports into consideration when improving best practices and guidance in current protocols – and aims to produce a concept paper by July that identifies areas for change. To start the process, the EMA has established two expert groups to carry out preparatory work. One group will look at pre-clinical aspects and the data needed to safely initiate first tests in humans; the other group will examine clinical aspects and how the design of first-in-human trials could be improved.

Although the French trial has put first-in-human studies in the spotlight, the EMA explains that such studies are usually very safe. Since 2005, approximately 3,100 first-in-human studies have been carried out in Europe and only one other severe incident has ever been reported. *JS*

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Failure to Launch

How difficult is it to develop a new drug? Statistics have the answer

Taking a promising drug all the way through to regulatory approval is a long, difficult process – and successes are rare. Most drugs fail before they reach the clinic, and most drugs that reach the clinic fail before approval. Diving deeper into the problem, the Biotechnology Innovation Organization (BIO) teamed up with Amplion (a biomarker business intelligence company) and BioMedtracker (a service that tracks a drug's likelihood of approval by the FDA). BIO examined clinical trial success rates from 2006 to 2015, and 9,985 clinical and regulatory phase transitions were recorded and analyzed from 7,455 development programs, across 1,103 companies in the BioMedtracker database.

The study revealed that phase II clinical programs continue to experience the lowest success rate of the four development phases, with only 30.7 percent of developmental candidates advancing to phase III. For all diseases analyzed, only around 10 percent of drugs in phase I trials made it to approval. However, the study also showed that using biomarkers as selection criteria could dramatically increase success rates. Our infographic gives more information. *JS*

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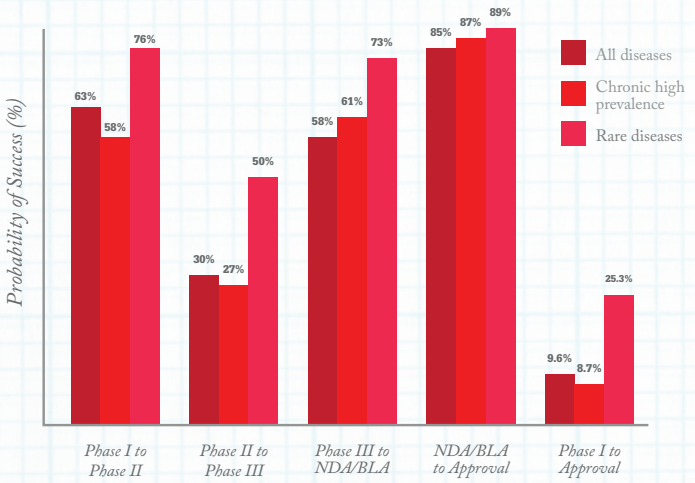


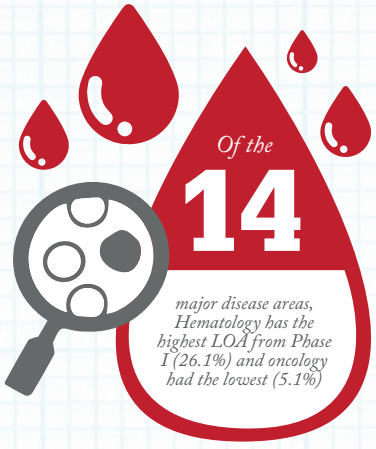
70%

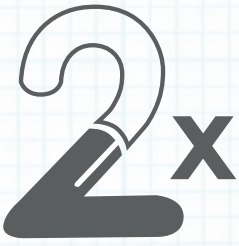
of developmental candidates do not advance to Phase III

The overall LOA from Phase I for all developmental canidates was

9.6%, & 11.9%

for all indications outside of Oncology





Oncology drugs had a 2x higher rate of first cycle approval than psychiatric drugs, which had the lowest percent of first-cycle review approvals

2x

Sub-indication analysis within Oncology revealed hematological cancers had 2x higher LOA from Phase I than solid tumors

Oncology drugs were also approved fastest of all 14 disease areas

LOA = Likelihood of approval

A Vouch for Caution

Will expanding the Priority Review Voucher scheme defeat its original purpose?

The FDA has issued priority review vouchers (PRV) to incentivize drug development for rare or neglected diseases since 2007 – and such a voucher is a valuable prize since it allows a company to expedite the review of any one of its new drugs by four months. The voucher can also be sold on the open market for millions of US dollars.

Many argue that the scheme has been a success – so much so that US Congress is looking to expand it to other areas. But is expansion necessarily a good thing? David Ridley, a professor at Duke University's Fuqua School of Business urges caution, as increasing the supply of diseases eligible for vouchers will increase the number of vouchers and decrease the price. "Lower voucher prices will mean lower incentives for innovation for diseases that are currently eligible for vouchers," he says.

The PRV program was developed based on a 2006 paper written by Ridley and his colleagues Jeff Moe and Henry Grabowski (1). "We had good luck in several ways, including timing. Congress passes major FDA legislation every 5 years (when FDA user fees are renewed), and 2007 was one of those years," says Ridley. "Potential voucher buyers were initially cautious because they didn't want to pay hundreds of millions of dollars based on an unproven voucher mechanism, but now there are many developers with funding and drugs in the pipeline thanks to the voucher incentive."

According to Ridley, the voucher price has risen from $67.5 million to $350 million – which is certainly a good incentive for a drug developer. The scheme has also been well received by both the industry and sponsors in Congress (particularly as the vouchers do not require the allocation of additional government funding). The list of diseases eligible for the PRV program was expanded earlier this year to incentivize the development of treatments addressing the Zika virus outbreak. Senators and representatives are also considering creating other PRV programs for generics and neonatal treatments.

Ripley hopes that members of Congress will be cautious about expanding the program. As an example, he has estimated that if only one priority review voucher is available in a year, it will be worth in excess of $200 million. If four vouchers are available, however, then the value could drop to below $100 million. *JS*

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Shaking Up European Drug Prices

Will future drugs in Europe be priced based on therapeutic outcomes?

For some time there have been rumblings in the industry of whether it is possible to price drugs based on how well they work. Indeed, the true therapeutic benefits of drugs have been in the spotlight ever since governments started to more closely assess the cost effectiveness of treatments and what could be funded by healthcare systems. In Europe, it seems as if the concept of a radical shift in pricing is under serious consideration. A document due to be discussed by the board of the European Federation of Pharmaceutical Industries and Associations (EFPIA) has been leaked that reportedly sets out a "roadmap for change towards outcomes-based reward systems". The leaked document was obtained by Reuters (1).

EFPIA was unaware that the document had been leaked until the publication of a Reuters article, but has acknowledged its existence, explaining that the document was developed in response to the affordability challenges faced by healthcare systems. Understandably, the association has been cagey about the details. "The internal EFPIA document referenced in the [Reuters] article was developed by a working group from across the EFPIA membership, to support continued dialogue with governments and healthcare systems in finding solutions to make medicines accessible and healthcare more sustainable, whilst securing future medical innovation," explained EFPIA in a statement (2). "In the future, we believe we can contribute to more sustainable healthcare systems by developing new pricing models, such as outcomes-based, or value-based contracts."

A pricing system based on outcomes would not be without risk to the industry. "If a product does not deliver on its clinical promise, society should not continue to pay for it," the document reportedly states. But on the flip side, it does mean that drugs that deliver high value will be rewarded. EFPIA adds that a number of countries have already started to develop outcomes- or value-based contracts. The document, however, suggests a more wholesale adoption of such systems. Another element reportedly discussed in the document is a move away from external reference pricing; currently, governments tend to examine prices in other countries to assess what they will pay for drugs.

The document is set to be discussed by the EFPIA board in mid-June. *SS*

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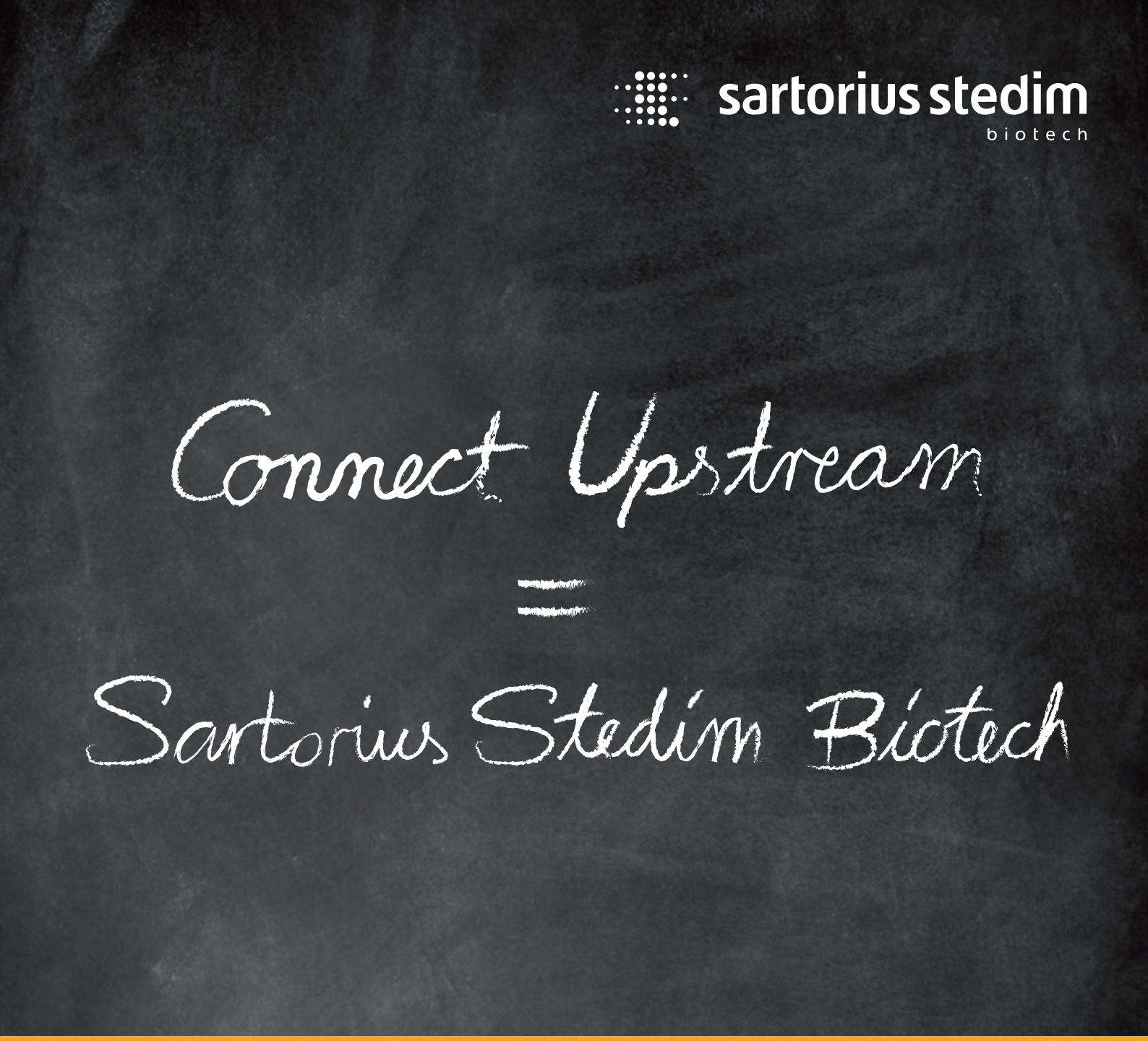

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In My View

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

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

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All Hail the ADC Heroes

Amazing innovation is happening all around us in the pharma industry. We should take the time to look outside of our own unique areas to congratulate the efforts of others.

By Christa Myers, Senior Pharmaceutical Engineering Specialist at CRB, USA.

The public doesn't always have a good view of the pharma industry, but truly this is an industry of heroes. In particular, there is a constant desire to improve rather than allowing a status quo for patient treatments.

In the last issue of The Medicine Maker, Vijay Chudasama (https://themedicinemaker.com/issues/0516/better-together) discussed the subject of antibody drug conjugates (ADCs). Most of us reading this publication are technical, but we're not experts in every single area; there are times when I think we need to sit back and remind ourselves of the incredible work done by scientists and engineers outside our own area of expertise. I mainly focus on facility design, but I'm a self-confessed fanatic of progress in our industry, so I like to see what is bubbling in other areas of drug development – and to shout out when I see something successful. I think we should all do the same.

ADCs fascinate me because their formulation is all about making good drugs work better, which links back to the desire to improve. Cytotoxic drugs can be highly effective against cancer cells – but can also damage healthy cells and lead to severe side effects. As Chudasama explained, ADCs consist of three components: an antibody that is built to target specific spots on the surfaces of cells, an active drug (often a chemotherapy), and a linker that is in place to prevent release of the drug until it is in exactly the right location. Only a small number of ADCs have received regulatory approval, but there is a great deal of excitement about the potential of these therapies – and much ongoing research.

But the complexity doesn't end with research and development; from a manufacturing perspective, each component of an ADC has a vastly different manufacturing method, which can lead to each piece of the ADC puzzle being made in different facilities. The antibody is a biotech product, the drug is usually a small-molecule API and the linker must be made via organic synthesis. The antibodies used in ADCs are manufactured using a monoclonal cell culture production that consists of cell culture reactions, harvesting and purification – the result is a bulk container of biologically active antibodies. The payload of the ADC is often made as

"ADCs fascinate me because their formulation is all about making good drugs work better."

an API in a classic chemical reaction and separation production train that results in a container of dried active drug product. Sometimes, this API is highly hazardous, which is an extra burden in manufacturing because the API must then be handled with extreme care and specialized equipment. As the conjugate is purified, the risk of exposure is reduced, but it is not completely eliminated. Each step requires special consideration – and you can never be too careful. Of course, you also need to think about any potential impact on end users too, such as patients or healthcare practitioners, who may handle the finished drug.

The final piece of the ADC, the linker, is usually an organic chemical reagent with activity to create strong crosslinking between the antibody and the payload. All of the pieces tend to come together at yet another facility that finalizes the conjugation of the antibody to the payload using the linker, followed by more purification steps and final sterile filtration into the dosage form. Oftentimes, the conjugate is stable but then lyophilized to improve its shelf life.

Bringing the ADC puzzle to completion is a complex activity, but despite the challenges and obstacles, I find it remarkable that such progress is being made – not just on the R&D side but also in terms of manufacturing. Companies are constantly looking to make the process as streamlined as possible.

It takes many heroes to bring all of these complex areas together to create a new drug that could make treating a disease less painful and more effective than the treatments of even 10 years ago. Most of us will know someone who has suffered cancer (in my case, it was my grandfather). At some point, perhaps I will have to face it too, but it's positive to know that drugs are being reformulated all of the time to make them better. Where will ADCs and cancer treatments be in another 10 years' time? It's an exciting thought. I'd like to offer my personal thanks to everyone working in this area. You're making the world a better place.

Codes, Drugs, and Rock 'n' Roll

Europe has set the stage for safer supply chains with its Falsified Medicines Directive. Next, the spotlight could fall on using serialization to boost patient centricity.

By Mark Davison, Principal Consultant at Blue Sphere Health Ltd, UK.

If the pharmaceutical industry was a 70s rock band, drug discovery would be the singer: high profile but temperamental (and doesn't always turn up). And the manufacturing and supply chain functions would be the bass player: essential but not typically a source of creativity or innovation (at least in the eyes of most executives).

The wave of new drug traceability laws might change that perception as manufacturing and supply chain function gets pushed into the spotlight. The European Union's Falsified Medicines Directive (FMD) and its similar counterparts worldwide (such as the Drug Supply Chain Security Act in the US) were drafted primarily to help prevent counterfeit medicines from reaching patients. The last pieces of FMD were published in February and have set off a three-year compliance period. There isn't space to discuss the wider nuances of FMD here, but there are two key packaging elements: tamper-evidence and unit-level traceability. All packs of prescription medicines must be sealed at the point of manufacture – surprisingly not a requirement before now – and must carry a scannable, pack-specific code, which FMD calls a safety feature. This 2D Datamatrix code must contain batch number, expiry date, a product identity code and a pack identity code.

These codes will allow drugs to be traced and checked across the EU using the European Medicines Verification System (EMVS), including during dispensing. Hopefully, the system will reduce counterfeiting by enabling rogue codes to be spotted – thus preventing harm and saving lives. Although no system can guarantee a watertight barrier against fakes, EMVS will greatly hamper the ability of counterfeiters to exploit the legitimate supply chain.

Machine-readable packs will also mean safer hospitals. Did you know that medication errors cause more harm than fake drugs do? Many incidents can be attributed to manual data entry mistakes or misreading of labels. Hospital practices mean the original coded pack may not always be present, but FMD will be an extra safety net for many key medicines. In the early hours of the morning, a handheld code scanner is always wide-awake, even if the nurse using it to check the strength and identity of a dangerous intravenous drug is tired and busy.

Keeping patients safe is the priority, but FMD and the new serial numbers

required on packs could also boost efficiency. Today, the pharma supply chain picture is pixelated. Thousands of packs with the same batch and expiry data are effectively indistinguishable clones. With the advent of FMD and the serialization requirement, we will gain unit-level vision, whereby each box or bottle coming off the production line will be unique. Because those codes are checked during dispensing, FMD should enable quicker and more focused recall of only specific packs (rather than the whole batch) – overall resulting in less waste and a faster recall response. Greater precision may also lower the risk of drug shortages, which can happen today following a full batch recall. For pharmacists, recalls will be managed in a more automated way with less impact on pharmacy workload. Beyond safety, there may be other, albeit more contentious, benefits to FMD too...

I believe that the commercial future of pharma lies in blending products and services in a more patient-centric way. FMD may provide a new route to that goal. Those soon-to-be-ubiquitous Datamatrix codes are easily visible and the data they contain is unencrypted – meaning they are potentially readable by any patient with a smartphone. The next logical step for FMD – as we digitize the supply chain – is to get patients involved. Coded packs provide a route to delivering approved information direct to a patient's phone, such as an electronic version of the patient leaflet. We all know that patient information can often be ignored (particularly small print) so why not send a reminder of safety-critical patient information as well? A dosage reminder service or prescription refill alerts might also be useful. Greater convenience and better information should lead to increased patient engagement with medical treatment and, hence, better adherence and improved outcomes.

Linking medicine codes to opt-in benefits and services could also lead to new business models. Safeguards will definitely be needed, and a flexible regulatory approach will be important, but we have an opportunity to add real value for patients. We don't need infeasible new technology – we already have the phones in our pockets. Investment by our technical operations colleagues in software, hardware, and services to get compliant with FMD means that the bass player is already tuning up.

Like most 70s rock bands, we in pharma find writing new hits difficult – and putting codes on boxes won't help us to find innovative drugs. But with some imagination, it might increase the benefit of our existing ones – for us and our patients. Playing the old songs better could be a handy tactic while our new product pipelines go in and out of rehab.

Thinking Outside the Tox

Decisions around toxicology testing must be made using scientific methods, not emotions or politics.

By Sandy Mackay, Head of Toxicology at Wickham Laboratories, UK.

Toxicology is the science concerned with the nature, effects and detection of poisons. In the pharmaceutical industry, the definition changes slightly to focus on assessing the safety of drug products – a crucial element of drug development and product release, whether for a new drug or a new indication for an old drug.

Traditionally, toxicology has gone hand in hand with animal testing, and it is true that a significant number of regulatory safety assessments use this approach. However, there is an increasing focus on the development of in vitro testing methods. And although both in vivo and in vitro testing are intended to assess the safety of medicines, they do diverge from one another; in vivo tests tend to look at systemic effects, whereas current in vitro methods generally only examine a specific biological process or function.

An example of the different approaches is the rabbit pyrogen test (RPT) versus the in vitro monocyte activation test (MAT). The RPT is a long established test that gives a qualitative indication of the presence of pyrogens (fever producing agents) in the test substance being examined. Over the last 20 years, RPT has seen significant decline because of the implementation of the Limulus amebocyte lysate assay (LAL), which gives a quantitative indication of the presence of endotoxins. Although the LAL assay has led to significant reduction in animal use, there are limitations on the types of pyrogens that can be detected. MAT has a wider range of detection abilities and is based on the human immune response. It could completely replace RPT in many cases and is a good example of an in vitro success story.

So are these new methods putting an end to animal testing? Not yet. Despite the successes of in vitro methods, there are areas of concern; for example, ensuring that the process for accepting methods is consistent across regulatory agencies. Particularly in respect to quality control assays, different national pharmacopeias have different standards for adoption. Some countries require that the in vitro method be at least as good as the animal method, but other countries may accept a less robust method simply because it replaces animals. In my view, these decisions need to be made using scientific methods – not emotions or politics. It is a disservice to patients to introduce any method that might make medicines or medical devices less safe.

In vitro methods are also challenged by complexity, particularly when it comes to regulatory toxicity studies, such as those falling under good laboratory practice. Potential interactions between whole body systems are extremely complex and not something that scientists can fully comprehend or simulate outside of the body right now. There has certainly been very good progress in replacing animal testing with in vitro tests that scrutinize one particular behavior, response or interaction, but replacing all animal tests is daunting to say the least.

The question of animal use is of course an important one, and those involved in such testing should endeavor to continuously replace, reduce, refine and be responsible in animal use where possible. That being said, our first and foremost goal must continue to be patient safety – and any new methodology should be assessed on that basis. We should all welcome increased scientific collaboration and public engagement on replacing animal testing – both are vital to a successful future for in vitro methods.

"Despite the successes of in vitro methods, there are areas of concern."

Breaking the Bioprocessing Mold

Manufacturers have gotten to grips with the complexities of batch-based bioprocesses, but breaking into the realm of continuous bioprocessing can lead to even greater efficiency.

In any production environment, it is generally accepted that there are eight sources of waste: defects, overproduction, non-utilized talent, motion, transportation, waiting, inventory and extra processing. Many industries have reduced their waste by turning to "Lean" thinking and 'one piece flows' – or continuous manufacturing. Continuous manufacturing can deliver higher productivity and more consistent quality in a smaller footprint, with shorter lead times; and this has revolutionized the automobile industry.

What about the pharma industry? Steps have been made to implement continuous processes for small-molecule drugs, but it's a different story for biopharmaceuticals. For the most part, continuous bioprocessing efforts have been limited to just a few steps, such as perfusion cell culture. Michael Egholm, Vice President/General Manager of Biopharmaceuticals at Pall, believes in much greater potential for continuous bioprocessing.

What inspired your focus on continuous bioprocessing?

Continuous bioprocessing has been a discussion within the industry for a very long time, but nobody has really done anything about it in terms of developing the necessary technologies. The analysis I did with my team showed that the benefits of continuous bioprocessing were so great that someone simply had to do something. We considered our options and decided, about eight months ago, to break the cycle by proactively investing in technologies that help realize the promise of continuous bioprocessing.

Of course, it is easier said than done. Continuous bioprocessing is a difficult field to break into; few companies are using it and few tools are available. As a long-standing supplier of high quality processing systems with a strong and loyal customer base, we knew that we had the technical capability to jumpstart this evolution of the biopharmaceutical industry. Not only is it a big transformation for us, but also for the whole biopharma industry.

What does the industry want from continuous bioprocessing technologies?

Economics are very important, but actually my biggest take-away from all of our customers is that people want robust platforms – meaning that they work every time. Reliability or robustness is desirable for any piece of equipment, but even more so in continuous technologies where the line, by definition, is running constantly. Platform technologies are also key because they keep the continuous process simple and avoid the need for optimization beyond some minor fine-tuning; in other words, implementing a continuous bioprocess is no longer about climbing a huge technology mountain. The technology can be rolled out and implemented quickly.

Some of the critical bottlenecks in both batch processing and continuous processing include centrifugation and/or depth filtration for cell removal and chromatography for primary capture. These are perhaps the least efficient parts of the bioprocess and are not easily convertible into a continuous process. New technology was needed to make this happen. To achieve continuous clarification, we've combined acoustic wave technology with depth filters into a platform technology that works across many different antibodies. The big question: is the industry ready for a full-scale system? It takes time for companies to become comfortable with new technology. Continuous bioprocessing is so new that I think it's important to first give people the opportunity to try out benchtop systems – and to feedback on what they need in a large-scale system.

How do you plan to overcome the challenges?

Focusing on continuous bioprocessing has been a significant game changer for Pall. To really understand continuous bioprocessing and to build up expertise, we opened a laboratory at our New England Center of Excellence in 2015. There, we have been running a continuous process all the way from bioreactors through sterile filtration of the purified drug substance. All of this is in a significantly reduced footprint of what it would have taken for batch processing.

I am very proud that we concluded our negotiations with FloDesign Sonics

in 2015. We now have an exclusive license for acoustic wave separation technology that allows cell removal or clarification to be performed in a continuous step without a centrifuge. From a regulatory standpoint, the process steps that impact the CQAs (critical quality attributes) in a continuous process are the same as the ones used in batch processing. We've launched three continuous enabling technologies so far: the Cadence Acoustic Separator (CAS) benchtop system (for continuous clarification), the Cadence BioSMB Process Development system (for continuous capture and purification), and the Cadence Inline Concentrator (for single-pass tangential flow filtration) And we've committed to launching more. Later this year, we plan to launch a full-scale version of BioSMB, and in 2017 we'll be launching a full-scale CAS system and the Acoustic Wave Separation Benchtop for perfusion.

"There are many advantages to going continuous; reducing waste and cost to name two."

It's a little scary to commit to these dates (but there's nothing like pressure to get something done!). The continuous bioprocessing puzzle requires many pieces and, since the technology is so new, it's crucial that we receive customer feedback to help us further refine the solutions. For example, the feedback we receive from our recently launched

benchtop CAS system will be invaluable when it comes to developing the full-scale system. Moreover, the benchtop system also allows users to become familiar with the technology before the full scale system is launched. If we'd just jumped straight into full-scale systems, we could have missed out on an invaluable opportunity to learn about what matters most to the industry.

What do you feel are the main benefits?

There are many advantages to going continuous; reducing waste and cost to name two. And regulators are also keen for companies to review their options – and that includes tools that enable ongoing quality monitoring. Nearly every other industry is using continuous processing so why can't biopharma also use it to achieve greater throughput at lower costs?

With batch-based processing, much of the equipment in a bioprocessing facility stands unused for most of the time. Continuous processing is about using the equipment all the time to perform processes on a much smaller scale, with a smaller footprint (usually around 70 to 80 percent smaller footprint compared with batch processing) – and the lower associated costs.

How has the industry reacted to your focus on continuous bioprocessing?

We've only been talking about continuous bioprocessing for around eight months, but the industry response has been really positive. We're seeing many of the major players taking steps towards continuous bioprocessing – whether it's just one step or the whole gambit. And everyone has their own bias or view on the major hurdles.

The challenges of continuous bioprocessing can only be solved if we work together. Batch-based processing has served biopharma and patients very well, but does not enable further process improvements. Eventually, the industry must update and improve its processes. I don't think everyone will adopt a fully continuous bioprocess stream, but there are some logical steps that can be taken, such as implementing a continuous process just for the clarification step, that can deliver enormous benefits and savings.

SUSTAINING THE BIOPHARMA BOOM

When an industry grows rapidly, innovative approaches are required to ensure sustainable growth. Here, we speak to leaders at Ireland's National Institute for Bioprocess Research and Training – NIBRT – to find out how a focus on talent, training and technology is changing the face of the field.

By Killian O'Driscoll, Projects Director at NIBRT

Talk to any manager in biopharmaceutical manufacturing and close to the top of their list of priorities is the ability to attract, develop and retain talent. The focus on talent is reflected in recent international industry surveys, which highlight a growing concern in finding the right engineers, scientists, operators, technicians and management to maintain the industry's strong growth (1, 2). So how can we help address this?

Internationally, more students than ever before are attending third-level education – and life science degree programs continue to be popular options. And yet many students leave university with little knowledge about the biopharma industry, and the excellent careers within biopharma manufacturing.

On the other hand, biopharma hiring managers tend to have a strong preference for candidates with degree relevant qualifications, as well as several years of biopharma experience, which is always going to be a finite resource. To help foster more talent, there is a need to promote better awareness of the career opportunities within biopharma to the public at large. Ask people to name just two biopharma companies and many struggle to do so – many pupils and parents are simply unaware of the rewarding career opportunities within biopharma. And yet we have a great story to tell; just think of the life-changing medicines that have been developed and how rewarding this type of career is.

The industry also needs to develop and grow its existing staff. Internationally recognized continuous professional development (CPD) and qualifications are a feature of other professions. And though global CPD programs have been tried sporadically in the past within biopharma, now that the industry's potential is fully established, perhaps it's time to re-visit such programs.

When looking for talent, we also need to look outside of traditional sources of supply. Schools of chemical and biopharma engineering can only produce so many graduates a year – many of whom will be targeted for recruitment well before graduation by large companies with the resources to offer and promote graduate programs. But we don't need to rely solely on degree students; there are rich veins of talent in other areas – those individuals with a vocational education background or from other industrial sectors may have many of the competencies required in biopharma manufacturing. For example, we've seen examples of tradesmen and workers from other sectors who, with appropriate cross training, go on to thrive in the biopharma manufacturing industry. Industry placements, internships and apprenticeships have a key role to play here (notwithstanding the logistical challenges of providing such placements).

A daring plan

In Ireland, the government decided that it was important to invest in biopharma after hearing about the growing importance of the industry at the start of the millennium. A tender process resulted in the decision to set up a national institute for bioprocessing research and training: NIBRT. Given the maturity of the sector at the time, this was a bold and brave decision – particularly as it involved an investment of 60 million euros – but the reasons were clear: the potential of biotech was recognized, as well as the need to establish a strong pipeline of talent.

NIBRT is a fully functional pilot manufacturing facility dedicated to training and research. Everything is done to GMP standard, but it gives people the opportunity to learn and to make mistakes. Industry send their staff to NIBRT for customized training programs and students from higher education institutes come here to get hands-on manufacturing experience. But NIBRT isn't just an institute to benefit Ireland – we also have a strong focus on international training and more than thirty percent of our trainees come from overseas.

NIBRT opened its doors exactly five years ago – in June 2011 – and we've been delighted with the success since then (training approximately 4,000 people each year). The industry continues to grow rapidly and it is very rewarding to be involved in developing the talent that will help the industry thrive.

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FINGER ON THE BIOPHARMA PULSE

With John Milne, Bioprocessing Training Director at NIBRT

Why is biopharma training so important?

In the 'good old' days, you finished your education, got hired, and learned on the job. But learning on the job isn't always convenient in today's fast-paced world, especially in a regulated and expensive industry. After all, mistakes in biopharma manufacturing can lead to the loss of an entire batch, equating to large losses in revenue. But if people aren't allowed to fail, then how can they learn? Students typically learn how to be good students at schools, colleges and universities, but the practical side of bioprocessing is more challenging – and the reality is that students rarely leave higher education equipped with the complete skillset.

In Ireland, NIBRT is integrated into the curricula of various university programs to give students hands-on manufacturing experience. Biopharma manufacturing is a very controlled, logical and often repetitive process. Most people, with the right attitude, can be trained to work well in this environment. However not everyone is suited to working with GMP and a lot of people don't like doing the same thing repetitively or working to such strict standards. Training also gives people the opportunity to see if bioprocessing is the right fit for them.

Would you say the industry is more open to graduates?

Being a graduate is not a prerequisite to being able to work in biopharma. I've seen people with no foundation at all still transition into various parts of the industry. Manufacturing is perhaps the most important area of the commercial biopharma industry. It can be overshadowed by research – but it is manufacturing that generates company revenues. There is often a shortage of skilled manufacturing personnel but it's a job that many people can learn and be trained to do well. There is also a great career path in manufacturing. Most people will start on the production line, which is the best way to learn, but they can also transition to other specialized teams or subsets of the facility as they gain more insight – perhaps into validation, process design or approval roles, or into roles designed to better understand bioprocessing. With these more applied roles come wider responsibilities and not everyone is suited for this. They require a different skillset to what is needed on the manufacturing floor and you need people who can respond to problems and make good decisions – without panicking. Once you move into quality, you need to really understand the science and associated regulatory requirements. If you are the person in charge of releasing a product then you could be the one going to jail if there's a problem!

What are the main drivers in biopharma manufacturing?

In its Process Analytical Technology Guidance released in 2004, the FDA introduced a concept that we've all become very familiar with today: Quality by Design (QbD). QbD has focused the industry's attention on process improvements, such as getting more product from process, resulting in lower costs and more predictable production. This is important because cost is a huge issue in biopharma production. Simply maintaining your license and keeping the operation going is a huge investment.

You can't always change the steps needed for biopharma production, but you can make them more efficient, such as by using smaller or more flexible equipment, or replacing stainless steel with single-use components. Even a small change can have a beneficial impact. When you're manufacturing a product in a bioreactor, you're actually making several versions of that product. There can be a lot of wastage and the industry has not quite figured out how to manipulate the cells to generate the one true product that is wanted. If you could make the cells make more of your product by even just 20 percent, it would save 20 percent of facility time per annum. The saved resources could be used to manufacture another product, which is important because another problem facing the biopharma industry is factory floor space. A lot of exciting biopharma products are coming down the pipeline, but where are they going to be made? Perhaps companies will come to Ireland to build increased capacity in a new facility, which addresses one issue, but a facility quickly gets busy. I think the increased use of modular facilities is definitely one way to go.

Is there any danger that a new facility may be out of date before it even opens?

Building a new facility certainly takes time and money, and designers have to base their plans on today's certainties rather than tomorrow's uncertainties. However, it's easy to invest millions of dollars into a fantastic looking facility that is then not fit for purpose in 10 years' time because the processes of the future are likely to be much smaller in scale. Right now, companies often need big manufacturing facilities because they have large patient bases for high dose products

"In terms of the basics, biopharma manufacturing is not rocket science. It is very controlled, logical and repetitive. Most people, with the right attitude, can be trained to do it."

BELIEVE IN BIOINFORMATICS

Moving from the cell to facility by developing data mining approaches for biopharmaceutical manufacturing

With Colin Clarke, Principal Investigator at NIBRT

What is your role at NIBRT?

I lead the bioinformatics and data analytics research group at NIBRT. My background is in bioinformatics, with a focus on the application of multivariate statistics and machine learning for the analysis of high dimensional datasets. My primary research interest lies in the utilization of these techniques to identify the fundamental biological processes that drive the production of recombinant therapeutic proteins in mammalian cell factories. I'm trying to understand how CHO cells grow to high density and synthesize large quantities of therapeutic proteins, or indeed why some CHO cells don't. Enabled by a Science Foundation Ireland (SFI) grant, we work with scientists here at NIBRT, the cell line-engineering group at the National Institute for Cellular Biotechnology, and international collaborators in the area to translate this understanding into increases in production efficiency. Industrial relevance is crucial to our research – and we have on-going partnerships with biopharma companies in Ireland, the UK and US.

Why did you go into this area?

I've always had an interest in computers and biology, and at the time the data explosion in biology was just beginning so it seemed like the natural route to take in my studies. Bioinformatics is now a critical component of biological science. The field has evolved at a remarkable pace, even in the short time since the human genome project. The development of next generation sequencing technologies in recent years has signaled the birth of a new era and pushed the demand for bioinformatics to new levels. It's a great time to be working in this area.

How does bioinformatics fit into manufacturing?

One of the big challenges for the biopharma manufacturing industry is prediction of outcome – and the more you know about the machinery of the cell factory, the closer you can get to being able to predict if a particular cell, or indeed population of cells, is going to perform well in large-scale bioreactors. At the moment, there is a lot of cell screening to find the best cells that will give the best performance, but there's a community of us that believe we can engineer a cell using gene-editing technology to build better cell factories. A better understanding of the biological system can also be used to better understand the potential impact of new production modes, such as continuous culture on cell performance. We know the smallest alterations in a process can impact the cells and there are many unanswered questions around how CHO cells will behave during extended culture. What happens when you start running processes continuously for longer periods of time? For instance, fed-batch culture processes running over a period of around 14 days are well established. If the culture runs for 50 or 100 days, can we maintain product gene expression?

What are you working on right now in CHO biology?

The CHO cell biology field is a relatively small community and there are few bioinformaticians working in this area. So we've been looking at the computational side and developing graphical user interfaces so that people who aren't experts in the field can analyze CHO cell next generation RNA sequencing data. In addition, we have a number of projects ongoing with biopharmaceutical companies examining model cell lines displaying desirable/undesirable phenotypes, as well as investigating the origin of specific production issues.

We are also developing algorithms for mass spectrometry in collaboration with Jonathan Bones' group (see Know Your Process, Know Your Product on page 28).

Are you applying your expertise in data analysis to other areas?

Yes, we have also started to look at the utility of "big data" technologies for biopharmaceutical manufacturing. For example, if you had the computational infrastructure to combine and analyze all the data generated in a manufacturing plant in one database, what questions could you ask? What could you understand about the process that you didn't know before? And is it possible to use predictive analytics to achieve optimal performance?

What's the future of bioinformatics in biopharma?

I think that data analytics is one area where the biopharma industry has a lot of catching up to do compared with other industries. If we look at car manufacturers, they're already onboard with big data technologies. Biopharma could really benefit from big data because there's so much variability in processes.

"Biopharmaceutical molecules are very challenging – and in 100 years' time they will still be challenging."

and there's no getting around that. Smaller manufacturers have an edge because they can take advantage of new smaller flexible systems – like single-use bioreactors – because they don't have to deal with the same volumes that big manufacturers have to contend with.

When designing a new facility, you have to consider potential demand. At the very start of production for a new drug, you may not immediately need huge bioreactors, but the initial decision is often made to invest in stainless steel because later demand is expected. Once you start producing and selling the drug, you can quickly make your investment back (assuming all goes to plan). Stainless steel is well proven and understood, but does it make for the most versatile, flexible plant?

Another problem for big companies is that there is often much competition. For example, Regeneron is building a large manufacturing facility in Ireland to scale up a drug that received FDA approval last year (Alirocumab – developed with Sanofi). It's a PCSK9 inhibitor designed to treat high cholesterol in adults. Immediately afterwards, Amgen received approval for their own PCSK9 inhibitor – Evolocumab – and Pfizer is also developing a similar product – Bococizumab – which hasn't yet been approved. Few companies are in the fortunate position of serving a patient base that no one else serves, so there's a constant race to market and battle for market share.

How can we battle the high costs of biopharma?

Pharma is a very attritional business. Just look at therapeutic monoclonal antibodies – we've had the technology in place for making them for over 40 years and yet less than forty molecules have gained regulatory approval.

Single-use technology is promising because of its potential to cut costs. You can build a operational large scale stainless steel plant for $500 million in around three to four years, but with new advances in single-use technology, you can build a facility with a potentially similar throughput (depending on how big your volumes need to be) in around two years at probably a fifth of the cost – which can get your product to the market faster. In spite of the many advantages, however, single use technologies are not without their challenges. Extractables and leachables from the plastic films are one concern and there is also the issue of available scaled systems. Would you really want to use a 10,000-liter single-use bag, even if one was available? Single use is also an ongoing consumable – and the costs can rack up. Manufacturers using single-use manufacturing strategies are also more dependent on their vendors and the wider supply chain in a way that hasn't been seen before. If a bioreactor bag comprises various components, which all come from different vendors, you're not relying on one vendor, but a whole network.

That said, there are challenges with stainless steel too, albeit we have a longer manufacturing history with these systems. Contamination can be an issue and the fact that you have to do the cleaning at all is a disadvantage in terms of clean utilities, time and talent – your workers are going to spend large portions of their time cleaning and turning around equipment between batches.

Any predictions for the future of biopharma manufacturing?

I heard an interesting prediction from someone recently – and I'll repeat it here. In 10 years' time, just looking at the production bioreactor as an example, the industry will probably be using 50/50 plastic/stainless steel. In 50 years' time, very few manufacturers may be using stainless steel. Biopharmaceutical molecules are often very challenging to manufacture and purify – and in 50 years' time they will still be challenging. We can collapse the required footprint, but cells will always be cells. There are some really interesting ideas about biopharma manufacturing being researched. For example, Thermo Fisher Scientific, the University of Maryland, Baltimore Country, Ohio State University and Latham Biopharm are collaborating to make biopharma medicines on demand. The grand aim is to be able to create medicines on battlefields for wounded soldiers, in remote locations, or in response to medical emergencies. The idea of moving away from being dependent on one large facility and instead bringing shipping and manufacture closer to the patient is something that is gaining increased attention across the entire pharma industry, particularly as we move towards personalized medicine, which will no doubt require regional centers. Greater utilization of continuous processing strategies are attracting wide interest due to their potential for improving the productivity of a process and reducing the facility footprint.

Is the hype around personalized medicine and cell therapy valid?

Earlier this year, there was a lot of media attention around T-cells after researchers claimed to have seen some extraordinary responses in patients with acute lymphoblastic leukaemia. Using the body's own immune system to fight cancer is very clever, but there is still much research to do. The technique the researchers were using was taking a patient's own T-cells, re-energizing them and then putting them back into the patient. How do you scale that up and perform cell therapy on a commercial basis? I think we're some way off seeing personalized therapy manufacture, perhaps it will be done in hospitals rather than manufacturing plants as we know them. While welcoming and embracing the potential of such therapies, we also need to be realistic. As an example, think about all of the hype we've heard about gene therapies over the years, but although thousands of clinical trials have been conducted, only a very small number of licenses have been granted.

With Jonathan Bones, Principal Investigator at NIBRT

How important is research at NIBRT?

Training is only one factor needed to build and expand biopharma's manufacturing knowledge base – research and new technologies are necessary to better understand biopharma manufacturing and the inner workings of cells, which will lead to improved manufacturing efficiencies.

As the name suggests, NIBRT is not just a training institute – we also have an active research program. The majority of what we do within the research team is applied research to solve the problems faced within the industry, as opposed to more fundamental basic research. Another important point is that the research team is based within a fully functional manufacturing facility. This is very useful for us – and also for the trainees who come here since we want them to feel at home. For industry partners, our facility replicates theirs and I think this helps to provide comfort and confidence that we understand their problems. And for those who have never been in a biopharma facility before, like university students, it's an opportunity to understand what the world of biopharma manufacturing is all about.

What is your research focus?

In my group, we study both the product and the manufacturing process. On the product side, we look at factors such as expressability and manufacturability of therapeutic proteins, and we also develop analytical technologies to characterize the different variants of the protein that the cell produces. We also have a significant interest in the characterization of the glycosylation present on these proteins also. I work in synergy with Colin's team (see Believe in Bioinformatics on page 26). We generate significant amounts of data and he helps us make sense of it all. Together, we're developing and applying a variety of analytical and bioinformatics technologies to better understand what's happening to and within cells during processing.

In terms of processes, we look at developing areas of analytical technologies and their practical applicability to better understand and control biopharma manufacturing. My group works hard on understanding how these platforms can be used to provide beneficial and meaningful information – but we also look at their limitations too. We're particularly interested in new separation technologies for intact protein analysis combined with high resolution mass spectrometry. We're aiming to close the loop on sequence confirmation and characterization of post-translational modifications to understanding the structural implications on the molecule and how they might affect its biological function.

"In terms of processes, we look at technologies and their practical applicability to biopharma manufacturing."

Working closely with Colin, my group is also very interested in the CHO cell proteome to understand cellular behavior during bioproduction and how this potentially affects product expression and product quality. Colin looks at CHO cells on the genetic level by looking at the genome and the transcriptome using advanced next generation sequencing technology. The information that his team generates is incredibly useful as they generate relevant databases and informative bioinformatics tools that facilitate more in depth proteomic studies within my group. Ultimately, our goal is to look at how cells respond to different conditions and to identify process indicator markers that may facilitate deeper process understanding and manufacturing process control. We're also looking at expressability and manufacturability to enable process streamlining once lead candidate molecules have been identified. Another area of interest is the application of single-use technologies, in particular, the characterization of extractable and leachable compounds and understanding their potential effects on CHO cell behavior.

You've also been developing 'PATsule'…

That's right – we've talked about this technology before (https://themedicinemaker.com/issues/1115/smart-sensor-capsule/). PATsule is a mobile sensing probe that will be able to move around the bioreactor to help therapeutic protein manufacturers better understand and control the process. Sensor probes are already available but they are fixed, which means they just measure one specific point inside the bioreactor. But what is happening at one point in the bioreactor might not be happening at another point. Cells are unpredictable after all…

We're working closely with our collaborators in the Tyndall National Institute who are currently developing the device, and we hope to begin live testing of the technology in bioreactors later this year. Working with the excellent engineers and scientists in Tyndall, we're moving fast with the technology. And I think there's a real demand for this kind of advanced process understanding.

Formulating for the Perfect Tablet Finish

When it comes to film coating, there's more than meets the eye. Is the drug or tablet core sensitive to acidity or moisture? What release profile is needed? And finally, how will the patient react to the finished product?

By Ali Rajabi-Siahboomi, Vice President and Chief Scientific Officer, Colorcon

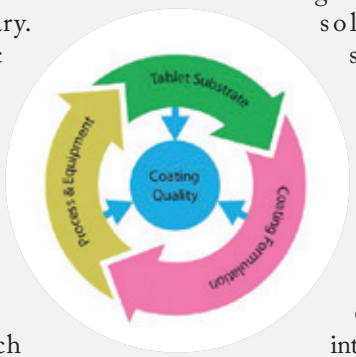
If you ask a consumer how they'd like to take their medicine or nutritional supplement, the chances are that they will pick a coated tablet over an injectable, liquid, or even a capsule. Coated tablets look familiar, are easy to handle and simple to consume. From the manufacturer's perspective, coated tablets facilitate branding and market differentiation, but also offer the potential to incorporate functional attributes for dose delivery. Selecting the right coating, however, can be surprisingly tricky. And getting it 'wrong' can impact patient compliance or even compromise drug efficacy by negatively affecting the release profile. At the start of any project, you need to consider factors such as taste masking, swallowability, desired release profile, regulations for the intended market – and aesthetic appearance.

Form and functionality

The choice of coating depends on the chemical properties and chemical nature of the tablet's core ingredients, including the drug or where it needs to be released in the body, sensitivity to the environment, and the physical properties of the drug's active pharmaceutical ingredient (API). Every drug is different so there is not a "one-size-fits-all" coating. That said, there are few core formulations, such as some orally disintegrating tablets, that currently may not be able to be coated – it is just a matter of understanding the properties of the tablet core formulation and matching the coating to it.

Enteric protection

From a functional aspect, an important consideration is whether a tablet requires protection from the acidic environment of the stomach – or indeed whether the stomach requires protection from the API. In either case, an enteric (or pH dependent coating) will be necessary. Aspirin (acetylalicylic acid) is perhaps the largest marketed drug that includes an enteric coating, but second on the list are proton pump inhibitors (PPIs), such as omeprazole, (prescriptions for which continue to soar). For patients taking PPIs, acid secretion in the stomach is inhibited, which makes the stomach pH increase. As most enteric polymers dissolve at the higher pH (5.5) than found in the stomach (pH 1.2), the coating should be able to protect the PPI at intermediate pH levels (for example, the drug should be protected even at pH 4.5 acetate buffer). Our datasets show that Colorcon's Acryl-EZE® II, an optimized aqueous acrylic enteric system, protects the drug at low and intermediate pH.



Moisture protection

Another common functional need of coating is moisture protection. Many APIs are poorly water soluble, so different technologies are used to enhance solubility; for example forming an amorphous drug from its crystalline (poorly soluble) form. These solubility improved drugs are moisture sensitive since they may convert back to their more thermodynamically stable crystalline form in the presence of moisture. Also, some drugs may degrade when interacting with moisture, so there is a lot of industry interest around moisture management for solid oral dosage forms. One raw material

excipient that we generally recommend for a moisture sensitive core formulation is Starch 1500®, partially pregelatinized maize starch, which has excellent binding capacity with water and thus reduces the availability of moisture to the API.

Coating formulation

We have also developed specific coating systems with moisture barrier properties, such as Opadry® amb II, a high performance moisture barrier film coating, which is a water soluble, pH independent dry powder film coating system for immediate release.

As soon as you know that your dosage is going to be formulated as a tablet, you should start thinking about which coating to include and begin working towards proof-of-concept in patients. It is well understood that many patients can't easily swallow tablets and don't like bad tasting formulations. Therefore the earlier you address these concerns, the better.

Connect with coating experts

When it comes to choosing and implementing the right film coating, don't be afraid to reach out to others with the right expertise. There are many products available and even if your choice makes sense in theory, you may encounter problems with implementation at either scale-up or production if you're not an expert in the area. Common areas for confusion include color and ingredient choice, as regulations for these vary by region and country across the globe. With expert insight, you're much more likely to get your coating right first time. To start companies off on the right path, Colorcon can provide not only innovative coating systems and expertise, but also formulation insight through our HyperStart® service. This online tool is freely accessible to provide a starting core formulation, film coating, and process recommendations. It's a great way to start the formulation and coating conversation and introduces important aspects related to development and processing early on.

Safety by design

The coating options available to pharma companies will continue to expand as new ways to improve the function and processing of tablets become available. As pharma moves towards continuous manufacturing, the process of coating will become faster and more efficient.

When you're in this field, it's easy to get caught up in the latest advances, but you should always remember to put the patient first. Without a high quality coating, tablets can erode or degrade in the bottle or packaging, stick to the throat, or leave a bad taste in the mouth. Even if a tablet doesn't need additional protection from light, moisture or acidity, it should at least be suitable for the patient to handle and swallow.

Keeping Up With Coating Trends

Pediatrics & geriatrics

These specialized patient groups have unique requirements related to taste-masking and ability to swallow medicaitons. For pediatrics, manufacturers are looking to make sure their coatings are safe for use in children and it is advisable to look for products that use raw materials that have precedence-of-use for pediatrics. Meanwhile, the growing number of geriatric patients, with inherent polymedication, points to an increased need for product differentiation, as many such patients take multiple tablets.

Natural colors

Some industries, including food and pharmaceuticals, are facing growing demand, through consumers, for "natural" or "clean label" products. Natural colors are used in coatings but tend not to be as stable as synthetic pigments. The industry is working to address this, and a greater number of natural colors are now available. Spirulina extract has recently been FDA approved for wider use in coating formulations applied to dietary supplements, drug tablets and capsules marketed in the US, expanding the natural color palette available to the industry worldwide.

Regulations

Recent focus on medication errors has led the FDA to release guidelines to address tablet differentiation. Also, regulatory agencies are encouraging manufacturers to think more about patient compliance, facilitated by good tablet design and coating inclusion.

Continuous manufacturing

As the industry seriously considers a transition from batch to continuous manufacturing, there is a need for coatings that are compatible with continuous processes operating at higher speeds – without compromising final tablet appearance. We've been developing coatings that can be sprayed much faster and that have higher levels of solid in the coating dispersions, which significantly increases productivity while still delivering the perfect finish.

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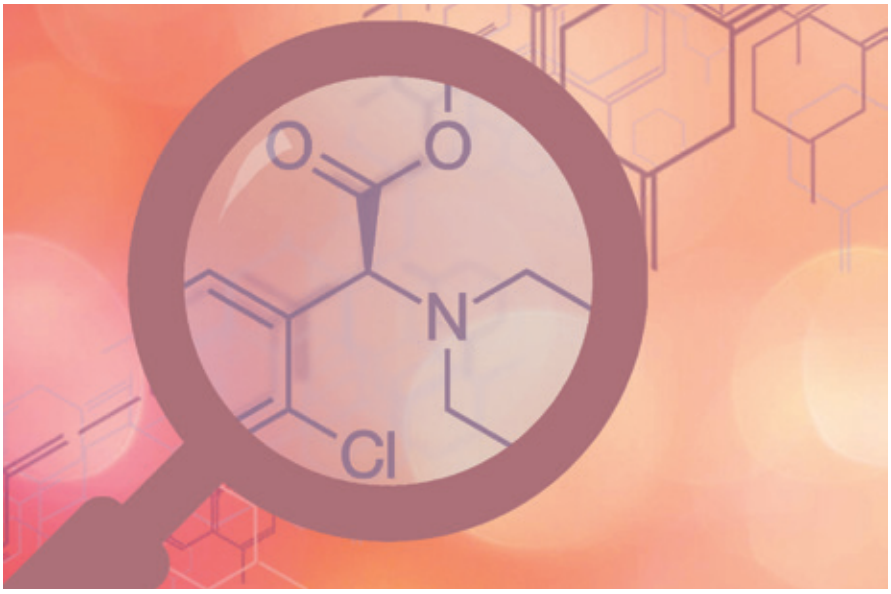
Insights into Elemental Impurities

Packaging components can leach into drug products and become foreign impurities. Guidelines exist for the testing of drug products for elemental impurities, but how are these applied to elemental impurities derived from drug product packaging?



By Dennis Jenke

Elemental impurities in drug products are impurities that either are or contain certain chemical elements – most notably those elements identified as metals and transition metals. The ICH Harmonized Guideline Q3D, Guideline for Elemental Impurities (1), notes in its introduction that "because elemental impurities do not provide any therapeutic benefit to the patient, their levels in the drug product should be controlled within acceptable limits". This is a logical observation, and the guideline (which applies to both new finished drug products and new drug products containing existing drug substances) presents a process for assessing and controlling elemental impurities. A related document, United States Pharmacopeia (USP) Monograph <232> Elemental Impurities – Limits (2), also specifies limits for the amounts of elemental impurities in drug products. Both have been aligned to provide a consistent position on safety requirements for elemental impurities.

Q3D and USP <232> represent an evolutionary – rather than revolutionary – advance in drug product impurity profiling. It has been a long-standing requirement that drug products be characterized for metallic impurities via the so called heavy metals test, so Q3D and USP <232> are not noteworthy in the sense that they introduce, for the first time, the concept of elemental impurity profiling. However, Q3D and USP <232> are noteworthy in that they establish more rigorous and quantitative test methods for drug product characterization, notably:

- Increased breadth (Q3D/USP <232> target a greater number of elemental impurities).
- Increased sensitivity (the Q3D /USP <232> methods are several orders of magnitude more sensitive).
- Improved focus (Q3D/USP <232> emphasize a "customized" focus on individual elemental impurities as opposed to total heavy metals).

It seems clear that implementation of Q3D and USP <232> will provide a more rigorous assessment of the safety of future drug products. However, a 'great unknown' in the implementation of these procedures is currently how the test results obtained by applying these evolutionary tests (and specifications) to existing drug products will correlate with compliance obtained via heavy metals testing. Indeed, until such products are tested via the new, evolutionary methods and held to the new specifications, the precise impact of the implementation of Q3D and USP <232> remains to be established.

Packaging systems are in intimate contact with the drug product, raising the possibility that packaging material components may leach out and become foreign impurities. Both ICH Q3D and USP <232> establish a drug product's packaging system as a potential source of elemental impurities and both documents note that "the potential contributions from (container-closure systems) should be considered to determine the overall contribution of elemental impurities to the drug product". However, neither document provides a specific or detailed means of determining and assessing a packaging system's contributions to a drug product's elemental impurity profile.

On the other hand, guidance on how to establish the presence of potential elemental impurities in packaging is provided by the USP in the form of various relevant monographs; in particular, USP <661> Plastic Packaging Systems and their Materials of Construction (3).

Looking into USP <661>

USP Monograph <661> notes that contact between plastic packaging systems and the packaged drug products "may result in an interaction between the therapeutic products and the packaging systems and its materials or components of construction" and further states that "these interactions must be such that the suitability for use (including safety and efficacy) of the therapeutic products and the packaging systems is not adversely affected by the interaction." The monograph establishes the tests and specifications that are needed to make sure that packaging systems are suitable for use – and accomplishes this via two associated Monographs, Plastic Materials of Construction <661.1> (4) and Plastic Packaging Systems for Pharmaceutical Use <661.2> (5).

While the two monographs – <661.1> and <661.2> – are logically connected and together support the development and use of packaging systems that are suited for their intended use, they address different aspects of plastic packaging systems characterization and/or qualification. <661.1> seeks to ensure that packaging systems are suited for their intended use by focusing on selection of appropriate construction materials. The concept is to avoid using candidate materials that could adversely affect the quality and safety of pharmaceutical products. By contrast, <661.2> considers the entire packaging system from a more holistic perspective. Correctly applied, each may produce data significant to a competent safety assessment.

Proper material selection

Focusing on materials of construction, <661.1> is based on the premise that "to ensure that a packaging system is suited for its intended use, it is important to select materials of construction which are suited for use in packaging systems." It adds: "intentional selection of well-characterized materials minimizes the risk that a system made from those materials will be unsuitable."

The overall objective of <661.1> is to "establish, with a degree of confidence, whether potential material candidates could adversely affect the quality and safety of pharmaceutical products." While <661.1> characterization establishes the composition or characteristics of the material and thus aids decision making about whether the material is an appropriate candidate for use in a packaging system, there is no guarantee that plastic systems constructed from materials meeting <661.1> specifications will be suitable for their intended use. As the monograph points out, "the actual qualification of the material occurs when the entire system is qualified for use in a particular application via <661.2> testing."

"Implementation of Q3D and USP <232> will provide a more rigorous assessment of the safety of future drug products."

Materials that have been tested by <661.1> methods and which meet the specifications therein are said to be "well characterized". The implication is that decisions concerning the use of the material in a specific packaging situation can be made and justified on the basis of the characterization data.

However, the data do not specifically or universally qualify the material for use in packaging systems, as the conditions of use can vary depending on the packaging application. It is the developer or user's responsibility to expertly review the <661.1> test results, as well as additional information as necessary, to decide if the characterized material is appropriate for its intended use. In other words, the intent of <661.1> is to provide information that enables decision-making, but not to make decisions!

The quest for elemental knowledge

Monograph <661.1> addresses elemental impurities by focusing on extractable elements (not total element content) because elements from plastics become elemental impurities in drug products only if they leach (or extract) from the plastic packaging component or system. Thus, while knowledge of the presence and amount of an element in a plastic is useful information, the more relevant information from the perspective of elemental impurities is knowledge of the element's leaching characteristics and potential.

To support the generation of this knowledge, <661.1> advises on:

- The means of generating and testing an extract.
- The "relevant" elements that must be targeted.
- The reporting thresholds (with regard to the outcome of the testing).
- The limits for specific metals consistent with specifications that exist in other pharmacopeia (typically non-safety).

The recommended methodology for extracting elements is the "standard extraction" – heating the sample in the presence of strong acid (0.1N hydrochloric acid). An acid extraction is justified by the generalization that elements, specifically metals, are extracted in their highest quantities in acidic media. The exact means of generating the extract (amount

Relevant or Irrelevant?

There is an interesting discontinuity between the capabilities of the screening test procedures for elemental impurities and the concept of "relevant elements". Elemental impurities that are present in packaging systems, which can leach from such systems and which could adversely affect patient safety, are clearly "relevant" elemental impurities. Elemental impurities that are not present in packaging systems, which cannot leach from packaging systems or are generally recognized as safe, are clearly "irrelevant" elemental impurities. Screening test procedures for elemental impurities quantify both "relevant" and "irrelevant" elemental impurities, so routine analysis of extracts could produce information on elemental impurities that are not strictly reportable per guidelines such as <661.1>. This opens the question of "what to do with the data for "irrelevant" elemental impurities?" As it is clear that information on "irrelevant" elements might be useful in making decisions concerning packaging for quality attributes other than safety, and that collecting data is a primary means for establishing what elemental impurities are irrelevant, users of guidelines such as <661.1> must recognize that it is not the guideline's intent to exclude "irrelevant" metals when data on such metals is readily available; rather, the guideline's aim is to ensure that proper focus is applied to the relevant metals.

of material per volume of acid, means of heating) is customized somewhat for individual plastic materials. Overall, the <661.1> methodology is designed to generate a 'worst-case' profile of extracted elements as few drug products will have a pH as low as that of the extraction solvent.

An element is deemed to be relevant (i.e., targeted for quantitation) in any of the following circumstances:

- If the element or substances containing the element are intentionally added to the plastic material.
- If the plastic material is contacted by the element or a source of the element during its production and it is possible that the element could be entrained in the material as a result of this contact.
- If the element is targeted in other pharmacopeia.
- If the element has been established in the elemental impurity guidelines as being an elemental impurity that is applicable to all drug product dosage forms, regardless of whether the element is intentionally added to the dosage form or not.

Note that although the driving force for assessment in the USP guidelines is safety, the principal driver in other pharmacopeias may be some other attribute.

For those elements that <661.1> targets for safety reasons, the monograph proposes a reporting threshold that is tied to a concentration of 0.01 mg/L in the extract; this level was chosen on the basis of a survey of laboratories well-versed in trace metal analysis. Since the extraction stoichiometry varies somewhat from material to material, material-based reporting thresholds (in µg/g) would be a less meaningful measure. For those elements that <661.1> targets because they are stipulated in other pharmacopeia, the limits specified in those pharmacopeia are reproduced in <661.1>.

The use of reporting thresholds by <661.1> assists in material selection. Thresholds, as opposed to limits, are particularly appropriate given the difficulties in aligning impurity limits for packaging with impurity limits for packaged products – difficulties which are exacerbated when one moves from packaging to materials of construction, as materials of construction are at least one step further removed from the packaged drug product.

Addressing safety – <661.2>

Of course, compliance with <661.1> tests does not guarantee that plastic packaging systems will be suitable for their intended use; it only enables a decision as to whether a given material is an appropriate candidate for use in a packaging system. Definitively establishing the suitability of a given material in a given application requires that the complete package system be tested in that application according to <661.2> guidance. Indeed, "the intent of <661.2> is to define and delineate the testing needed to produce the data required for establishing the packaging system's safety"(5).

Monograph <661.2> establishes that the chemical safety assessment required for a packaging system must address the relevant elements established in the elemental impurities guidelines, and should also consider the relevant permissible daily exposure (PDE) values contained in those guidelines. However, it is not necessary – and is largely inappropriate – for <661.2> to interpret the drug product PDEs in relation to allowable levels of impurities (or impurity generating entities) in packaging systems because of the great diversity of packaging systems, as well as storage and distribution conditions. Establishing limits that would be applicable in every circumstance would be impractical.

Moreover, the "proper contribution" that a packaging system can make to a packaged drug product's elemental impurity profile varies case by case. In one extreme, where other contributors to a product's elemental impurity "use up" a product's entire PDE, it is clear that the elemental impurity limits for the packaging system would need to be a very small portion of the product PDE. At the other end of the spectrum, where other contributors to a product's elemental impurity use up only a very small portion of the entire PDE, then elemental impurity limits for the packaging system could be a very large portion of the product PDE. Each particular drug product will sit in the continuum between these two extremes and its place on the continuum cannot be established by solely testing the packaging system, as this does not address the other contributors to the packaged drug product's impurity profile. Therefore, any attempt to establish a fixed portion of the PDE that is allowable for, or assigned to, the packaging system in all cases would be an arbitrary exercise.

By not specifying limits for extractable elemental impurities for packaging systems, <661.2> embraces the spirit of the elemental impurity guidelines: though PDEs are an appropriate tool to use in the safety risk assessment of elemental impurities, comparison of exposure levels to PDEs does not necessarily represent the only means to comprehensively assess safety in all cases. Circumstances associated with individual situations may dictate how PDEs are used in a risk-based process of safety assessment.

Strictly necessary?

It may be legitimate to ask if elemental impurity guidelines are actually necessary for plastic packaging. Guidelines to establish and limit the presence of extractable elemental impurities in plastic packaging systems are necessary only if (a) plastic packaging systems contain sources of elemental impurities and (b) the elemental impurities are leached from the packaging at high enough levels that they could adversely affect the safety of patients who receive the packaged drug product. A recent review of published information concerning the levels and extractability of elemental entities from plastic materials commonly used in pharmaceutical packaging systems (6) concluded that:

- Sources of elemental impurities are not typically intentionally added to plastics used in pharma packaging.
- Sources of elemental impurities are rarely accidentally or unintentionally present in plastics used in pharma packaging.
- Only a small fraction of the total amount of elemental entities present in plastics used in pharma packaging is leached into the packaged drug product under the conditions of production, storage, distribution and clinical use.

If these conclusions are valid over a wide range of materials and situations, then elemental impurity profiling of plastic packaging materials, components and systems by screening (meaning looking for elements which may or may not be present) may not provide a greater assurance of drug product quality or safety – which in turn could indicate that scouting might not be required by pharmacopeia or regulatory guidelines. Alternatively, targeting intentionally added or otherwise known elemental impurities and their sources could provide a greater assurance of drug product quality and safety – which in turn could indicate that targeting should be required by pharmacopeia or regulatory guidelines.

Although the existing information is compelling, it is not currently definitive enough to justify the reduction in or the elimination of elemental impurity profiling of plastic packaging materials, components or systems. But will this change in the future? Testing materials, components and systems using the methods and specifications contained in <661.1> and <661.2> will produce an extensive body of information and it may be that the preponderance of evidence that this information represents will support the reduction or elimination such testing. We will just have to do the testing and evaluate the results to establish the proper path moving forward.

Dennis Jenke is Distinguished Scientist at Baxter Healthcare Corporation, USA.

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Finding Fingerprints of Biosimilars

After finally breaking into the US market, biosimilars have created a real buzz in the industry, but the best practice for demonstrating similarity can be daunting to say the least.

By Fiona Greer

In most cases, it is relatively straightforward to prove that a generic small-molecule drug is the same as the originator product thanks to standard analytical chemistry and bioequivalence. Biologics, on the other hand, require head-to-head studies that prove the biosimilar is sufficiently similar to its originator in terms of structure, quality, safety and efficacy.

Biosimilars have been available in Europe for more than a decade, during which time the original 2005 biosimilars guidelines have been regularly updated – and in addition to overarching directives on quality, clinical and non-clinical requirements, there are product or class-specific guidelines for certain molecules (1). The European market is already being targeted by many non-European manufacturers, and numerous other countries worldwide have published and promoted their own pathways for biosimilars (many have chosen to adopt or adapt the European guidelines). The World Health Organization has also got in on the act by publishing guidelines on the evaluation of similar biotherapeutic products (SBPs) in 2009; supplementing these in March 2016 with a specific draft document on the evaluation of monoclonal antibody SBPs (2, 3).

The US was late to enter the biosimilars arena, with the introduction of the Biologics Price Competition and Innovation (BPCI) Act in 2010, which proposed the 351(k) pathway of the Public Health Services Act. It took another two years for the FDA to issue guidance for biosimilar manufacturers wanting to use this pathway, and further time for finalization; biosimilars have only started being approved in the country within the past year (4,5). As an accelerated pathway, 351(k) grants access to licensing based on a comparison with a reference product that has been approved via the standard 351(a) pathway. At the discretion of the FDA, a full suite of clinical trials may not be required for the biosimilar, as long as similarity to the originator is proven beyond "residual doubt." Provision is made for a second tier – interchangeable biosimilars – if additional clinical studies are successfully conducted.

Proving similarity

Both clinical and non-clinical data are used to determine similarity. The basis of the biosimilar fingerprint is a statistical approach that demonstrates the two products are analytically similar, but some product attributes are more important than others. Data for the first tier, representing critical quality attributes, should include a statistical equivalence test to prove comparability, and the FDA recommends that these should include those attributes that pose the highest risk when different. A good example in some molecules may be the protein's glycosylation pattern – the presence of sugars (oligosaccharides) attached to certain amino acid residues – or protein content. Second tier attributes are still important, but less critical, and quality ranges based on standard deviations may be appropriate for these. Those quality attributes in the third tier are the least critical, so graphical or raw data are likely to be sufficient.

The first step in proving biosimilarity is to determine detailed structural information for the originator molecule, which can then be used as a structural template for the putative biosimilar. It is important that many different batches of the originator are studied, as variation is likely to have occurred over time. The source of the reference product can also be an issue, particularly when developing a biosimilar for a global market, as some countries' regulators will only permit proof of biosimilarity to a batch from another country if appropriate demonstration is made to show that it is indeed representative of the authorized product in the country of application.

Developing a fingerprint for a biosimilar involves the use of multiple orthogonal analytical techniques, with appropriate quantitative ranges.

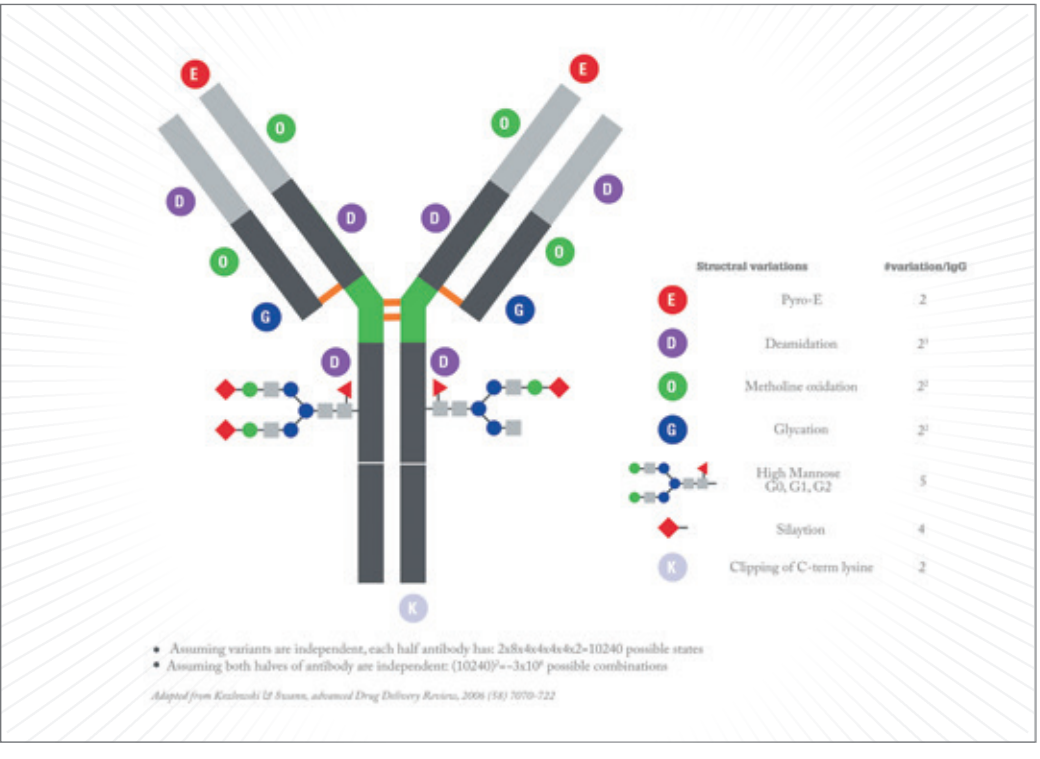

Figure 1. Example of complexity in the case of an antibody.

The similarity toolkit

ICH Topic Q6B lays down test procedures for setting quality specifications for biological drug products. It demands multiple physicochemical and structural analyses, and is an excellent starting point when determining a strategy for proving biosimilarity. Six specification requirements for structural characterization are mentioned:

1. amino acid sequence
2. amino acid composition
3. terminal amino acid sequences
4. peptide map
5. sulfhydryl group(s) and disulfide bridges
6. carbohydrate structure (if appropriate).

There are also six specifications for physicochemical properties:

- molecular weight or size
- isoform pattern
- extinction coefficient
- electrophoretic pattern
- liquid chromatographic pattern
- spectroscopic profiles.

Many different analytical techniques and tools can be used to obtain and collate this information, from classical chemical methods to newer, more advanced techniques, such as ion mobility mass spectrometry and hydrogen–deuterium exchange mass spectrometry (see Table 1 for a list). If the molecule is an antibody for instance, there are many types of interrogation that could and should be applied to structural comparison with the reference. The intact molecule can be studied, amino acid composition determined, and both N and C terminal sequencing carried out – a process that may require more than one peptide mapping enzyme digestion. The oligosaccharides attached to the heavy chain can be investigated, and the higher

The Analytical Challenge

Celltrion cited a number of analytical methods in its successful European application for approval for Remsima (a biosimilar to infliximab). The primary structure was assessed using:

- liquid chromatography-mass spectrometry (LC-MS) peptide mapping
- LC-MS intact mass measurements
- amino-acid analysis/molar absorptivity studies
- N- and C-terminal sequencing.

The higher order structure was assessed using:

- FTIR
- differential scanning calorimetry
- circular dichroism
- free thiol and S–S studies
- antibody arrays
- X-ray crystallographic techniques.

The oligosaccharide profile, N-linked glycan, sialic acid and monosaccharide analyses were used to identify glycosylation patterns. Purity and impurities were investigated using:

- size exclusion chromatography (SEC)
- SEC with multi-angle light scattering (MALS)
- analytical ultracentrifugation
- capillary electrophoresis-SDS studies.

The charged isoforms were assessed using isoelectric focusing (IEC) and IEC-HPLC.

order structures determined.

Glycosylation is perhaps one of the most important post-translational modifications (PTMs) that occurs during the manufacture of a protein as it may affect the antibody's efficacy and, in some cases, result in immunogenicity. PTMs such as glycosylation cannot be predicted from the gene sequence and have to be determined experimentally. Furthermore, the unpredictable addition of sugars greatly adds to the heterogeneity of the biologic medicine. As an example, just one immunoglobulin G type molecule has been estimated to have $3x10^8$ potential variations (see Figure 1). One technique that can be applied here is electrospray ionization (ESI) mass spectrometry, which can provide insight into the number and nature of carbohydrates that are attached on both the reference drug and the biosimilar.

ICH Q6B describes the need to study the carbohydrate content, the structure of the carbohydrate chains, and the glycosylation sites. Strategies analogous to those used for peptide mapping can be applied; for example, the glycoprotein can be analyzed intact or digested to form glycopeptides to detail the sites of glycosylation. Carbohydrate can also be released from the protein backbone. The resulting glycans can then be analyzed using chromatography and mass spectrometry.

Higher order structure

The conformation of the biologic also has a bearing on its activity and is another important area of investigation when developing a fingerprint for biosimilarity. Again, many techniques – both qualitative and quantitative – can be applied to determine higher order structure. One of the most commonly applied quantitative techniques is circular dichroism, which is sensitive to helix content, providing information about both secondary and some tertiary structure. On the down side, the presence of buffers in the formulation can interfere with the results. Fourier transform infrared spectroscopy (FTIR) is another quantitative method for secondary structure determination that is sensitive to sheet content and less likely to be affected by buffers.

"Glycosylation is perhaps one of the most important post-translational modifications."

Both intrinsic and extrinsic fluorescence techniques are used – the former for local tertiary structure, and the latter for surface hydrophobicity – but only give qualitative results. Other qualitative methods include differential scanning calorimetry, which looks at thermal stability, and UV-vis spectroscopy for local tertiary structure. An emerging technique from research applications, hydrogen–deuterium exchange mass spectrometry, highlights details of dynamics, conformation and interactions, but is expensive and has significant data processing requirements. Another technique more normally applied in a research setting is two-dimensional protein nuclear magnetic resonance.

The way that biologics oligomerize and aggregate must also be studied. Sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) is an inexpensive but low-throughput tool for assessing aggregates, and dynamic light scattering (DLS) can be used to look

Property To Be Determined	*Available Methodologies*
Amino acid sequence and modifications	Mass spectrometry, peptide mapping, chromatography
Glycosylation	Anion exchange, enzymatic digestion, peptide mapping, capillary electrophoresis, mass spectrometry
Folding	Mass spectrometry S-S bridge determination, calorimetry, hydrogen deuterium exchange and ion mobility mass spectrometry, nuclear magnetic resonance, circular dichroism, Fourier transform spectroscopy, fluorescence
PEGylation and isomerization	Chromatography, peptide mapping
Aggregation	Analytical ultracentrifugation, size-exclusion chromatography, asymmetric field flow fractionation, dynamic light scattering, microscopy, transmission electron microscopy
Proteolysis	Electrophoresis, chromatography, mass spectrometry
Impurities	Proteomics, immunoassays, metal and solvents analysis
Subunit interactions	Chromatography, ion mobility mass spectrometry
Heterogeneity of size, charge, hydrophobicity	Chromatography, gel and capillary electrophoresis, light scattering, ion mobility-mass spectrometry, capillary electrophoresis-mass spectrometry

Table 1. Potential analytical tools.

for high-molecular weight aggregates. Oligomers and aggregates can both be investigated using sedimentation velocity analytical ultracentrifugation (SV-AUC) and size-exclusion chromatography with multi-angle light scattering (SEC-MALS), both of which give quantitative results.

The science of safety

It is not sufficient merely to assess comparative structure: comparative functional assays also have to be performed. Suitable quantitative biological assays have to be developed and run to link product attributes with biological properties – and the results for the originator and biosimilar must correlate well if similarity is to be accepted by regulators. The assay must also be able to assess properties appropriate to the nature of the biosimilar. Again, a range of techniques can be applied, including biochemical assays, such as ligand binding, immunoassays, enzymatic assays and radioimmunoassay studies. Others are cell-culture based, including cytotoxicity, cell uptake, proliferation, secondary messenger and PCR-based functional assays.

The chosen techniques, both structural and functional, will vary from one biosimilar to another. However, the resulting information should always cover a sufficiently wide range of parameters to give regulators confidence that the biosimilar will behave in a similar fashion to its reference product in patients. For an example of how many different techniques may be needed for one product, see "The Analytical Challenge".

With the inevitable variability between biologic products manufactured in different cell lines, careful comparative studies are essential if regulators are to be convinced that a biosimilar is both safe and effective. By applying multiple orthogonal analytical techniques to both the reference originator product and the biosimilar, including functional studies, an all-important fingerprint of biosimilarity can give confidence that patients will not be adversely affected if they are prescribed a biosimilar instead of the originator product.

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Bioavailability by Design

Few oral biologics have made it to market, and though the challenges are well known, the benefits are huge and the task is not impossible. New technologies can help.

Many promising new drugs are working their way through clinical development, but bioavailability remains a major challenge for the industry. As is typical in successful development, tackling problems early can make a big difference and lead to optimized timelines. In 2015, Catalent launched a toolkit of technologies – the award winning OptiForm Solution Suite – that was designed to help overcome bioavailability challenges for early-stage small molecules, by pairing their characteristics with suitable drug delivery systems. But what about large biomolecules? Enter the OptiForm Solution Suite Bio, which specifically addresses bioavailability challenges faced in biologic development – with a focus on the 'holy grail' of oral delivery. Stephen Tindal, Director, Science and Technology at Catalent, tells us more.

How has the industry reacted to OptiForm Solution Suite?

In general, very favorably; companies particularly like the data-driven concept. The OptiForm Solution Suite is all about applying rigorous science to better understand the structure of a molecule and how it might interact with drug delivery technologies that are needed to help with solubility or bioavailability problems. The data can be used to rank options early on and to allow developers to make better-informed developmental decisions. After all, making the wrong decisions concerning a drug delivery technology for a molecule can cost months of extra time, delaying the project. Data from the OptiForm Solution Suite helps justify both to management and regulators why a certain drug delivery technology was selected. Overall, it's about providing confidence that the right technology was selected from the start, which makes the drug development process smoother.

What common challenges plague early drug development?

Early characterization and optimization work are crucial, but need to be placed into context with the challenge of drug delivery. If an API is unstable at a given pH, this could change the delivery approach and technology employed. Also, there can be a temptation to work only with the technologies which are familiar, rather than reaching out for external expertise.

What are the specific issues around developing oral macromolecules?

Many companies have considered OptiForm Solution Suite to help them with poorly soluble small-molecule APIs. Macromolecules' solubility is less of a concern – the main problems are usually poor absorption due to the size of the molecule, as well as the molecular geometry and lack of flexibility. Macromolecules which can't squeeze through tight spaces won't be absorbed into the body because of the permeation limitations of the tight junctions in the gastrointestinal (GI) tract and limited transcellular pathways. In addition, macromolecules demonstrate low stability in the GI tract, so although they're soluble they tend to be degraded by the harsh acid environment or enzymes before you get any permeation.

"We will definitely see more commercially successful oral biologics in the coming years."

Only two peptides have been licensed for systemic oral delivery – cyclosporine and desmopressin. And because of limited success, people may come to the assumption that it's too difficult to make an oral macromolecule product, particularly given the pressure on time and resources in today's industry. However, we are seeing increasing interest in this area. Few (if any) patients like injections (the delivery method for the majority of biologic medicines), which is one of the reasons why we set up the Catalent Applied Drug Delivery Institute. Indeed, a major area of focus for us is on non-invasive macromolecule delivery.

How has OptiForm® been adapted to work with macromolecules?

The new add-on for the Suite – OptiForm

Solution Suite Bio – rapidly screens macromolecules to assess stability issues and the potential for delivery via the oral route. The material for the first animal study can be ready in as little as 3 weeks. Even though the biggest problem is permeability, it is possible to enhance this. For example, chemical modification could improve absorption in the small intestine, or permeation enhancers could help the macromolecule pass through tight junctions. In order to help with stability, enteric coatings are also a popular choice, and there may be protection from a lipid formulation as well. As part of OptiForm Solution Suite Bio, we look at whether our proprietary drug delivery technologies – OptiGel Bio or Zydis Bio – can help by performing tests to assess compatibility. A report is produced that delivers the data and suggests potential developmental routes, to exploit any positive findings.

Our drug delivery technologies aim to enhance the ability of macromolecules to be delivered orally. Optigel Bio is a lipid formulation with safe and marketed ingredients and formulation options, which accelerates complicated clinical and regulatory pathways. An enteric coating protects the capsule from gastric rupture and thus the macromolecule is protected from enzymatic degradation until it is released with the permeation enhancer to help open up tight junctions for the large molecule to pass through. Only minimal amounts of permeation enhancer are used and the tight junctions recover within 15 minutes to prevent unwanted substances from reaching the blood. Meanwhile, Zydis Bio is an Orally Disintegrating Tablet (ODT) (made through lyophilization) that dissolves in the highly vascularized mucosae within the mouth to give pre-gastric absorption, thus avoiding first-pass metabolism.

The oral delivery of macromolecules has been described as the 'holy grail' of drug delivery. Is it within reach?

It may be. We may see more commercially successful oral biologics in the coming years. However, there is a broad range of macromolecules in terms of size and it will be very challenging to deliver the largest molecules this way; for smaller peptides there is definitely room for optimism. Having access to a toolbox of technologies that target different biological barriers and help screen for oral delivery potential is a big step forward. Catalent Applied Drug Delivery Institute leads the Non-Invasive Macromolecule Delivery Consortium (NMDC) to help connect people who have the expertise to help each other, but also to begin the process of providing innovative solutions. The next Non-Invasive Drug Delivery of Macromolecules Conference, held by NMDC, will be in San Diego (California) from February 21 to 24, 2017, where experts from academia and industry will discuss the new updates for non-invasive macromolecule delivery technologies. We are only at the beginning of our journey towards oral macromolecule delivery, so we're very excited to contribute to the new delivery technologies of the future.

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Pharma Manufacturing? There's an App for That

Mobile technology and apps have become a staple of the pharma industry in terms of disseminating information to patients. Much less is known about their impact on manufacturing, but thanks to developments in cloud computing, the sky's the limit.

With George Mashini

I've always specialized in – and been fascinated by – information technology. I actually started out writing software code for the types of backend systems run by large manufacturers, such as their enterprise resource planning (ERP), manufacturing and execution platforms. It was complicated stuff – and I liked it! Eventually though, I became curious about how my code was being used in the field, which was a real eye-opener.

Companies understand that they need IT systems, but they don't always understand how to fully exploit them – and perhaps with good reason; traditional IT infrastructure is based on purchased hardware and software, which means it can take time to implement and adjust to in a large company. Around eight years ago, some colleagues and I came up with a theory: looking at the way that companies procure, and considering their IT infrastructure and technology, it was clear that change happens very slowly. However, human beings want more flexible ways to interact with their work – and mobile technology has changed the way we interact very rapidly. We saw a real need for a new kind of flexible IT technology.

Into the cloud

Around the same time that we were considering how to act upon our theory, we saw the growing rise and acceptance of the "cloud." In cloud computing, applications, data and services are hosted over the Internet and can be accessed on demand. At first, there was apprehension about this way of working. On the one hand, cloud computing signifies cost savings because you are using cheaper resources that are being managed by somebody else, but on the other hand it signifies a loss of control – for the exact same reason. Today, however, you'll find cloud computing being happily used by many companies. I think we can all say that the cloud is a pleasant way of working. No longer do we have to be at our office desks to get work done – we can work from any location and can even access the same data using phones or tablets. But this is only the tip of the iceberg. Since cloud computing has become more mainstream,

"Companies understand that they need IT systems, but they don't always understand how to fully exploit them."

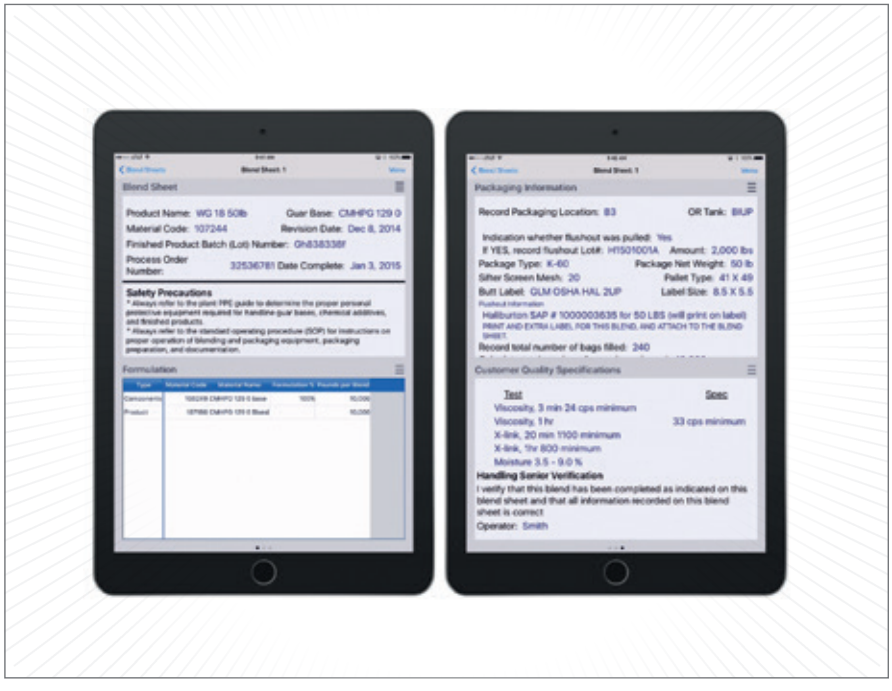
a number of vendors have popped up to take advantage of the technology by developing specialized platforms and apps.

Pharma companies are certainly aware of the potential of apps, but only in certain areas so far.. For instance, most pharma companies have invested in apps that help disseminate information to physicians and consumers, and sales reps have also been armed with mini marketing tools. In this area, pharma's use of mobile technology is very mature – and there has also been a lot of discussion around the potential of mobile health – or mHealth (see Apps Around the Industry on page 49). If we delve deeper into the operations and inner workings of a pharma company, it's a different story. Mobile technology can be used to help boost business efficiency by increasing employee productivity or better controlling inventory, for example. But right now, uptake is not even close to that seen with mHealth. Frankly, there is a very good reason for this. As pharma is heavily regulated, companies spend a lot of time and resources in implementing validated systems to run their business and manufacturing operations. There hasn't really been the opportunity (or the time) for them to innovate in this area. As I mentioned at the start, when it comes to IT infrastructure, things tend to change very slowly.

Nevertheless, appreciation of the problems faced by pharma companies continues to grow. Advances in mobile technology mean that, instead of completely overhauling existing infrastructure, it's possible to put a more modern interface over the top that allows the whole system to be used in a more modern and intuitive way.

Bringing clarity to manufacturing

There are a growing number of apps that can be rolled out in pharma manufacturing.



These are Blend Sheets, used to make sure that ingredients, formulation, packaging and quality are to spec. The instructions may be in different places or in different forms, so combining them into a single app is powerful.

Mobile Rise

- In 2017, the number of mobile phone users worldwide is expected to reach 4.77 billion (1). To put that into context, the world's population is expected to rise to 7.5 billion by 2017.
- Smart mobile phones are capable of carrying out many of the tasks we'd typically use a laptop for. In 2015, Wired magazine made a prediction that smartphones could completely replace computers within a few years, adding that the global PC industry has been on a downward trend for some time (2).
- Almost any task can be performed on a phone using an 'app' and indeed there seems to be an app for everything, from booking restaurants, to finding maps, to making lists, to telling you (in a pirate accent) where you parked your car.
- In pharma, mobile health (mHealth) is a buzzword and there is huge potential for the pharma industry. According to industry estimates, by 2018, 50 percent of 3.4 billion plus smartphone and tablet users will have downloaded mobile health applications (3).

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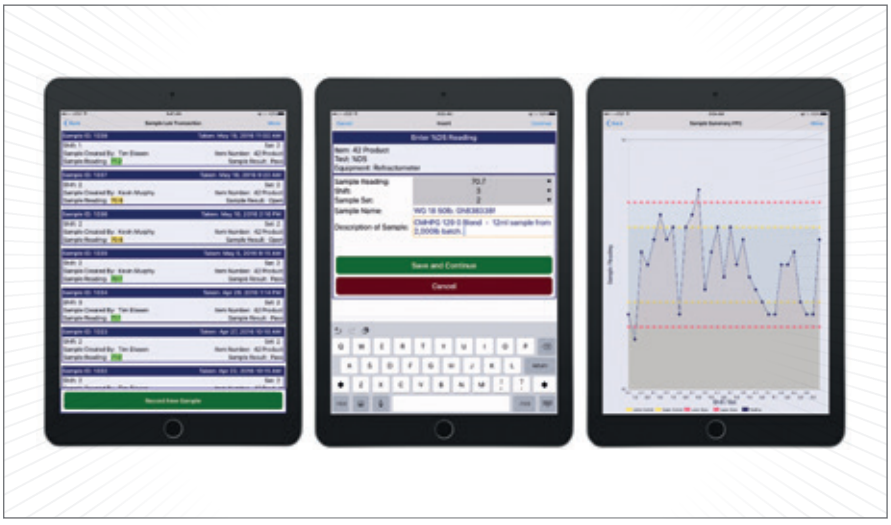
How to Make a Good App

- Identify the value. It's no use making an app for the sake of it – it must have a purpose.
- Identify who will use the app and then design it around their needs – consider how the technology will integrate with the user's job function.
- Keep it simple. It may seem like a good idea to stuff your app with as many features and capabilities as possible – but end users want to get their job done and nothing else.
- Allow the end user to have input into the design of the app – an app is useless unless it's used.
- Keep the focus on the functional aspects of the app. Deciding on whether something is 'good' can often depend on a variety of factors, such as performance and aesthetics. But for an app, it's the users who decide if your app is good or not. And the most important criteria is to make the app useable and functional.



"There are perhaps hundreds of ways in which mobile technology can better improve employees' daily lives."

Historically, manufacturing managers would plan in the morning, and then review what happened the day before the following morning. They'd create a new plan accordingly, for example, increasing or decreasing throughput. Over time, each square foot of the facility is used more efficiently, and the experience allows more agile decision making in the future. Apps can accelerate this process because they can be designed to interpret data from multiple systems within a manufacturing environment, giving a clear picture of what is happening in real time on the plant floor – and they can alert someone if something is out of specification. Such real-time information can be used to more efficiently deploy the workforce where it is needed throughout the day.

Another potential area for apps to make a mark is in maintenance. When something goes wrong, there is inevitably a considerable amount of wasted energy as the engineers investigate the problem, search for a solution, consult with specialists, locate repair manuals and finally order new parts. Apps can provide a toolkit for engineers that includes manuals, repair videos, warranty information and details about parts – all in one place. And it can be accessed on the plant floor via a tablet or smartphone.

These two examples are very broad and can apply to any manufacturing organization. Neither of them reinvent the wheel but they are examples of how apps can help support leaner operations. And the beauty of apps is that they are pretty easy to create. If you have an idea, then an app provider can probably make it happen. As an example, I worked with a company to develop an audit management tool. During FDA inspections, the company found that people had to be taken out of their jobs to be 'available' because everyone had different pieces of information. Audits are necessary, of course, but there can be a loss of productivity while they occur. The new app we created virtualized the audit; a live stream indicates what is needed for the audit and alerts are sent out to the right people. Instead of everyone

involved sitting idle in a conference room, staff can continue working at their desks until they receive a notification telling them they are needed – and what piece of documentation is required. Moreover, the person coordinating the audit can view the status of the message, such as when it was received and when the person had confirmed they were on their way. It also better served the FDA auditors, because they received the information in a timelier manner. Although this isn't an 'off-the shelf' app (there are very few specific to the pharma industry), it does demonstrate what can be achieved with some creative thinking.

Reaching for the sky

Cloud computing is a great platform – and the sky's the limit as to what we can potentially do with it. But it's not up to vendors as to what gets created – the main creative thinking needs to come from the pharma manufacturers themselves. There are perhaps hundreds of ways in which mobile technology can better improve employees' daily lives. And as people become more used to the tech and what it can do, they'll have more ideas of how they can use it. People are generally quite comfortable with apps now in their everyday lives, but there can be a concern when it comes to using them within a business. Remember though, deploying an app is not the same as deploying a whole new IT infrastructure (apps are much more flexible). How long it takes actually depends on a company's own internal process for implanting innovation. If a company is innovative, agile and selects the right tools, then a simple but significant app can be implemented in less than a month.

The way we do commerce today is likely to completely change in the future because of the ongoing innovation in mobile technology. At the moment, mobile is where the Internet was in 1994. In 1994, it was difficult to explain to people how important the Internet would be and why they needed to get on board – but today, it's ludicrous to think of an office without the Internet. In the future, it will be equally absurd to consider working life without apps. In some industries, the future has already arrived.

This article was written based on a conversation with George Mashini, CEO of Catavolt, USA.

Apps Around the Industry

- Sanofi developed its GoMeals app to help patients, particularly diabetics, make healthy decisions about their meal choices. The app provides facts about food, such as calories, tracks the number of calories burned and helps patients monitor glucose levels. It also has a restaurant locator that allows you to browse menus to find healthy meal options.
- GlaxoSmithKline has developed several patient-focused apps, including an app to support patients with asthma (which includes advice and monitoring tools) and an app to help people quit smoking. The company has also developed apps for children, such as one that encourages children to brush their teeth by using superhero characters.
- Bayer has developed a pollen forecast app that allows users to see local pollen forecasts, track the severity of their symptoms, and read advice.
- The US Centers for Disease Control and Prevention has released dozens of apps. Examples include a guide to help physicians decide on the correct antibiotic regime for a sexually transmitted disease, and an app that examines influenza-like activity across the US.
- The World Health Organization has created several apps, including a pediatric app designed to help doctors, nurses and healthcare workers care for children in developing countries.
- In the UK, the Medicines & Healthcare products Regulatory Agency has released an app that allows users to report side effects to medicines.
- The FDA hasn't released any apps of its own – but to offer guidance in the area, it released the Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff in 2013. The FDA only deals with apps that present a risk to patients if they don't work as intended, as well as apps that may impact on the performance of traditional medical devices.
- The pharma industry isn't the only one looking to engage patients with mobile technology. There are countless apps available that target health – and more are released on a daily basis. In particular, technology companies, such as Google, Apple and Samsung, have all released health-related apps in addition to smart devices to track exercise and heart rate.

Trial Trailblazer

Sitting Down With... Ibraheem "Ibs" Mahmood,
President and Chief Executive Officer, DrugDev,
founded in the UK and headquartered in King of Prussia, PA, USA.

You have a degree in medicine... How did you end up in business?

I originally wanted to study science and math but my ambitious (and pushy) parents wanted me to go into medicine – so I did. I loved the theory, but I became disillusioned by the clinical realities. I remember diagnosing a little girl with a rare medical condition called Rhett Syndrome. I was proud of myself, and when I told the consultant doctor about my diagnosis he congratulated me. But then he told me that she'd be in a wheelchair by 15 and dead by 20; All we could do was manage the condition. I was totally dissatisfied with that.

I decided that I wanted to be involved in getting new medicines to doctors. Naturally, my first thought was research – my father worked at the Wellcome Trust in the UK for 30 years and my mother researched HIV at the UK's Medicines Research Council. But my parents told me I didn't have the patience for research, so I went into business.

I actually started in strategy, which wasn't very interesting, so I got into finance. Finance has a bad reputation, but it's really important. Think of the great scientists and entrepreneurs; the air they all breathe is money. Granted they may have noble intentions, but they also need capital. I learned that when it comes to investing in science, half the battle is finding the right financial structures to make something happen. I spent a lot of time at pharma companies before starting my own company.

What inspired your interest in the cost of clinical trials?

The biggest challenge in making medicines isn't discovering exciting molecules, it's cost-effectively bringing them to market. Many of the big pharmaceutical companies have an embarrassingly large number of extraordinary, life-changing molecules just sitting on their shelves, but testing them all would be too expensive. I'm not a researcher so I can't develop a new medicine and save lives, but I realized that if the costs of trials could be reduced, then more trials would be conducted; more medicines would be brought to market – and more lives would be saved! The key? Finding the right investigator, which can be remarkably difficult.

We began with that simple concept: making it easier to find good investigators for clinical trials. We developed a sort of 'LinkedIn' system where registered investigators could upload their professional history and look for clinical trial opportunities. We discussed the idea in 2008 and by 2011 we had 67,000 registered clinical trial investigators. It turned out to be a very valuable resource – and pharma companies loved it.

But is that enough to bring down costs?

With our data, we can recruit a full complement of investigators within a week or two – whereas it could take a pharma company months to do the same thing. But that was only the starting point of DrugDev. After the database was launched, someone in pharma told me that he loved what we were doing, but he described it as giving him 'plumbers' when he wanted to 'build a whole house'; we were only fixing one problem in the clinical trial conundrum. What if we could do more?

Lots of small companies have come up with best-in-class solutions to individual problems in clinical trials, but they've never reached critical mass. We've been bringing these together and integrating them to automate the clinical trial process. For example, you can have software with supporting services that allows a pharmaceutical executive to configure the clinical trials that they want to run, and then at the other end of the system, a person is receiving instructions for how to run the trial. And suddenly everyone comes together like a very efficient army. Automation doesn't sound very sexy, but automation can halve the cost of clinical trials. In addition, when you collaborate and bring lots of modern solutions together in an efficient way, you start to see new insights, including the potential to almost standardize the clinical trial process.

"Automation doesn't sound very sexy, but automation can halve the cost of clinical trials."

What are your hopes for the future?

People often say that nothing ever changes in the industry. There's some truth in that, but I believe the industry has never been under more pressure than it is now. But there's so much room for improvement in the clinical trial process. For example, the classic way of communicating with a site and implementing a change at a site is to contact your head of clinical trials, who then contacts your country manager, who contacts your local monitor, who then goes to the site and makes the change – usually feeding back after a few weeks. It can all happen rapidly if everyone logs on to the same computer system. It may sound obvious, but it isn't happening at the moment. I hope that we will see the emergence of a clinical trial operating system (hopefully from DrugDev – but I'm open to competition!).

What's the most important thing you've learned during your career?

Good people are the most important aspect of starting a company. You've got to get yourself a kick-ass team! And you've got to understand what motivates them – and then create the best possible environment.

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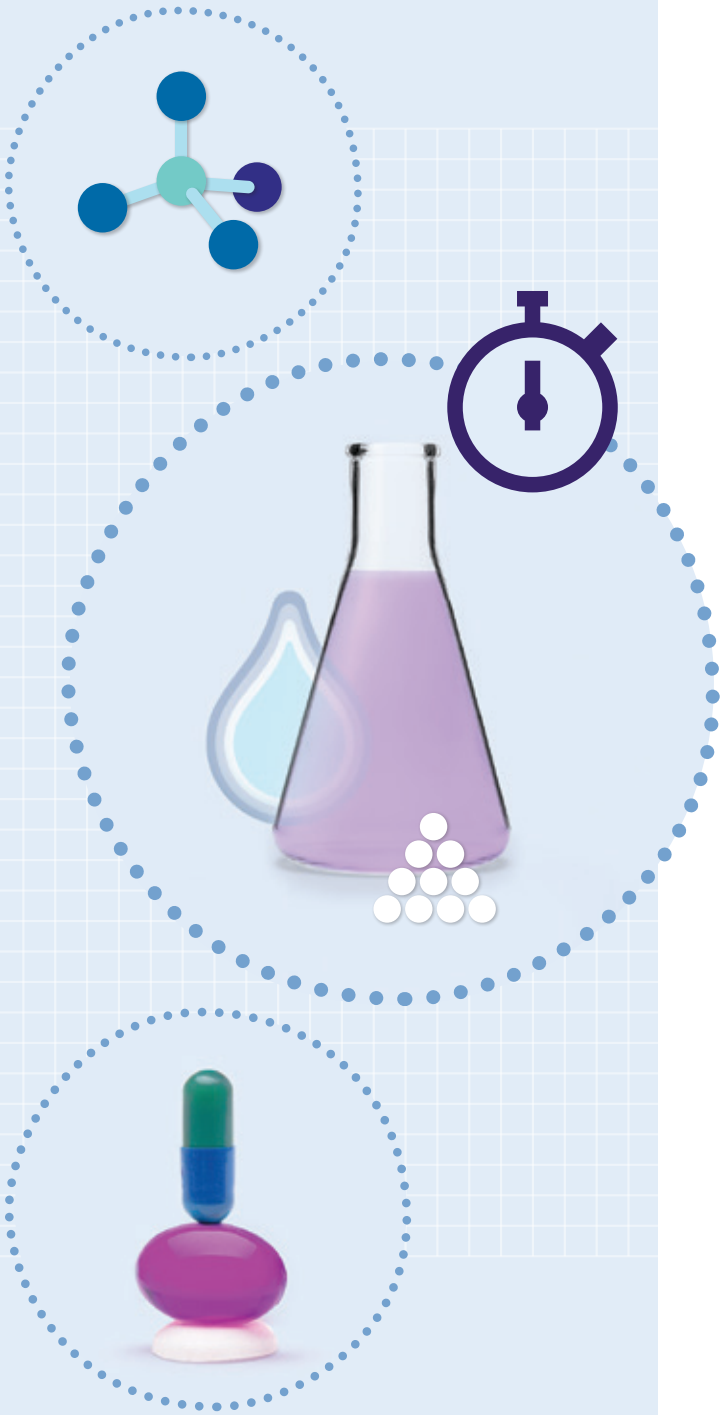

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