AUGUST 2018 # 44

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18 – 25

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Nominations for The Medicine Maker annual Innovation Awards are open until November 2, 2018. The Awards will showcase the most groundbreaking innovations for pharmaceutical development and manufacture released during 2018. Take a look at our website for more details.

http://tmm.txp.to/0618/innovationawards

Pharma Fiction

Pharma's reputation strikes again. A new Netflix comedy series is set to debut, featuring "two strangers [who] find themselves caught up in a mind-bending pharmaceutical trial gone awry."

Let's be honest, a fictional series is unlikely to capture the realities of clinical trials or the pharma industry, but the trailer has caused quite a stir in the entertainment world. The series is called Maniac and will launch globally on Netflix on September 21, 2018.

http://tmm.txp.to/0818/maniac

Hope for Alzheimer's Disease?

On page 40, we ask experts why Alzheimer's disease has proved to be such a challenge for the pharma industry. But has a clinical trial finally seen success? A clinical trial of Biogen and Eisai's experimental BAN2401 drug seems to show some positive results, but a few questions have been raised about the different dosing groups in the trial.

http://tmm.txp.to/0818/alzheimers

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Too Many Cooks

Thought that most companies understood good manufacturing practice? Think again – there are always a few bad eggs

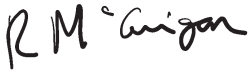
If you follow our monthly cartoon, "Trials of a Medicine Maker" you may be familiar with the character of Pat – a chef who accidentally finds himself in the bioprocessing lab, tasked with monitoring and controlling inherent process variability (tmm.txp.to/0118/Pat). We obviously intended this to be a joke, but one US company seems to have taken the idea far too literally.

An FDA warning letter was recently issued to Californian company BioDiagnostics after it was found to be using "kitchen cooking pots and household power tools" to manufacture a drug product in "filthy conditions." The investigator also found that there was an employee food preparation area within the manufacturing area, "with no separation between open manufacturing equipment, cooking utensils, and personal-use items" – a truly horrifying state of conditions in which to prepare a hemostatic solution intended to stop bleeding following cervical biopsy (1).

It seems ridiculous for any pharma manufacturer to be so clueless. In fairness, truly shocking Warning Letters are rare, but there are clearly companies out there who veer widely from standards, reminding us of the importance of regulatory oversight. Whether it's making sure paperwork and basic testing is up to date or preventing companies from storing everything in the manufacturing lab – even the kitchen sink – regulatory agencies are essential to patient safety. And that brings me to another recent announcement: the EMA has said that it will be further scaling back and suspending a number of its operations as the agency relocates from London to Amsterdam in preparation for Brexit (2). The agency now expects to lose around 30 percent of its staff, but there is still a high level of uncertainty and the figure could be higher.

Thankfully, regulatory inspections are not listed as being affected by the EMA's plans, but with Brexit causing such high levels of staff loss, it could still prove to be a recipe for regulation disaster. The fact that the agency is being forced to suspend any activities at all is a concern – and if the EMA finds itself even more hobbled by the impact of Brexit, who knows what the consequences could be for patient safety?

Roisin McGuigan
Deputy Editor



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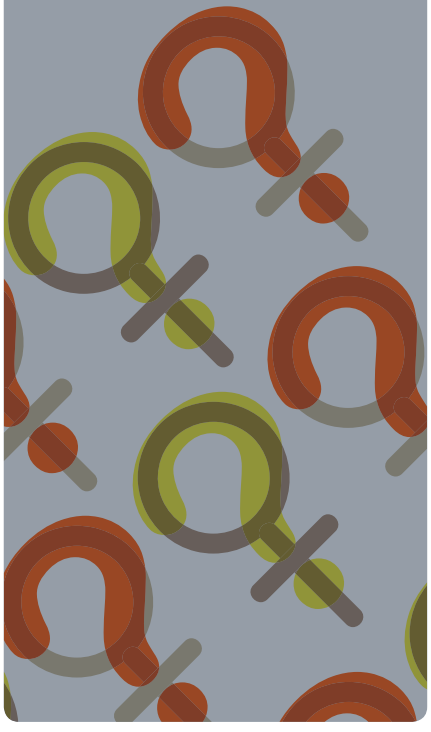
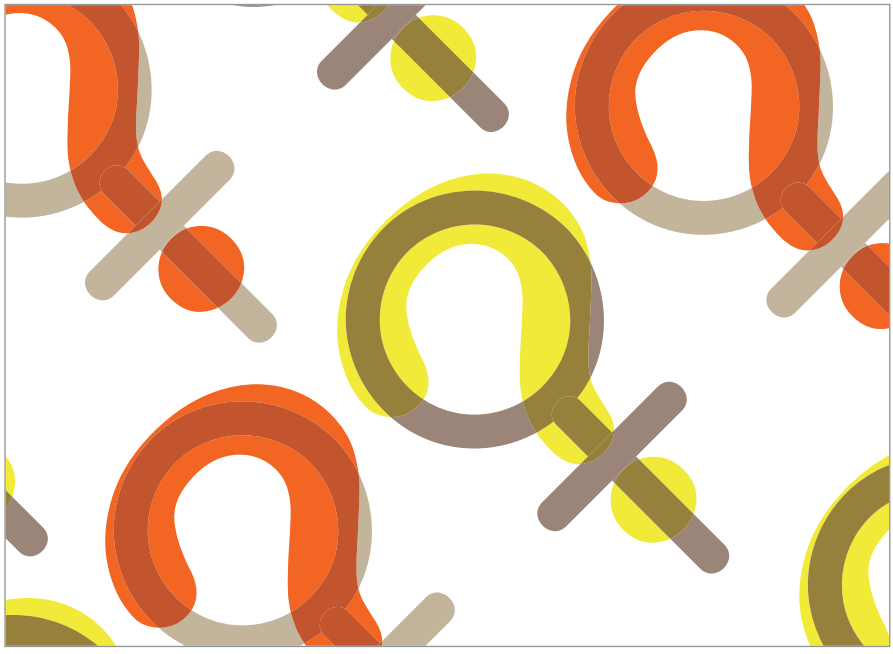
Upfront

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

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





What Women Want

Women, like men, want good medicines that have been tested in clinical trials involving fair representation of both sexes

The under-representation of women in clinical studies is a topic that comes up time and again. The FDA annually reviews the extent to which women are enrolled in clinical trials supporting new molecular entity submissions, led by the agency's Office of Women's Health, and there is definitely an upward trend; women made up 39 percent of late phase trial participants in 2000, but by 2015 this had risen to 52 percent. However, numbers of female participants are significantly lower in cardiovascular trials; for example, acute coronary syndrome, coronary artery disease and heart failure.

Marjorie Jenkins from the FDA's Office of Women's Health and co-authors recently examined women's participation in pivotal cardiovascular disease trials submitted to the FDA in support of marketing applications (1). "In recent surveys of coronary artery disease and ACS trials, participation of women ranged between 25 and 33 percent. Under enrollment of women in these areas has been attributed to under enrollment of elderly patients and the presence of comorbidities, such as diabetes," says Jenkins.

Men tend to have more heart attacks than women, but women have a higher heart attack death rate and experience higher bleeding rates during percutaneous coronary interventions performed through femoral arterial access. Women are also more susceptible to drug-induced cardiac arrhythmias.

Although women were under-enrolled in several cardiovascular disease areas, the absolute number of women who participated in the clinical trials reviewed was still sufficient to inform FDA approval of safe and effective cardiovascular drug treatments for both men and women. "But a better understanding of the reasons why women are not invited, or if invited do not

participate, could lead to more successful engagement and recruitment of women in clinical trials and result in increasing participation of women in certain clinical trial areas," says Jenkins.

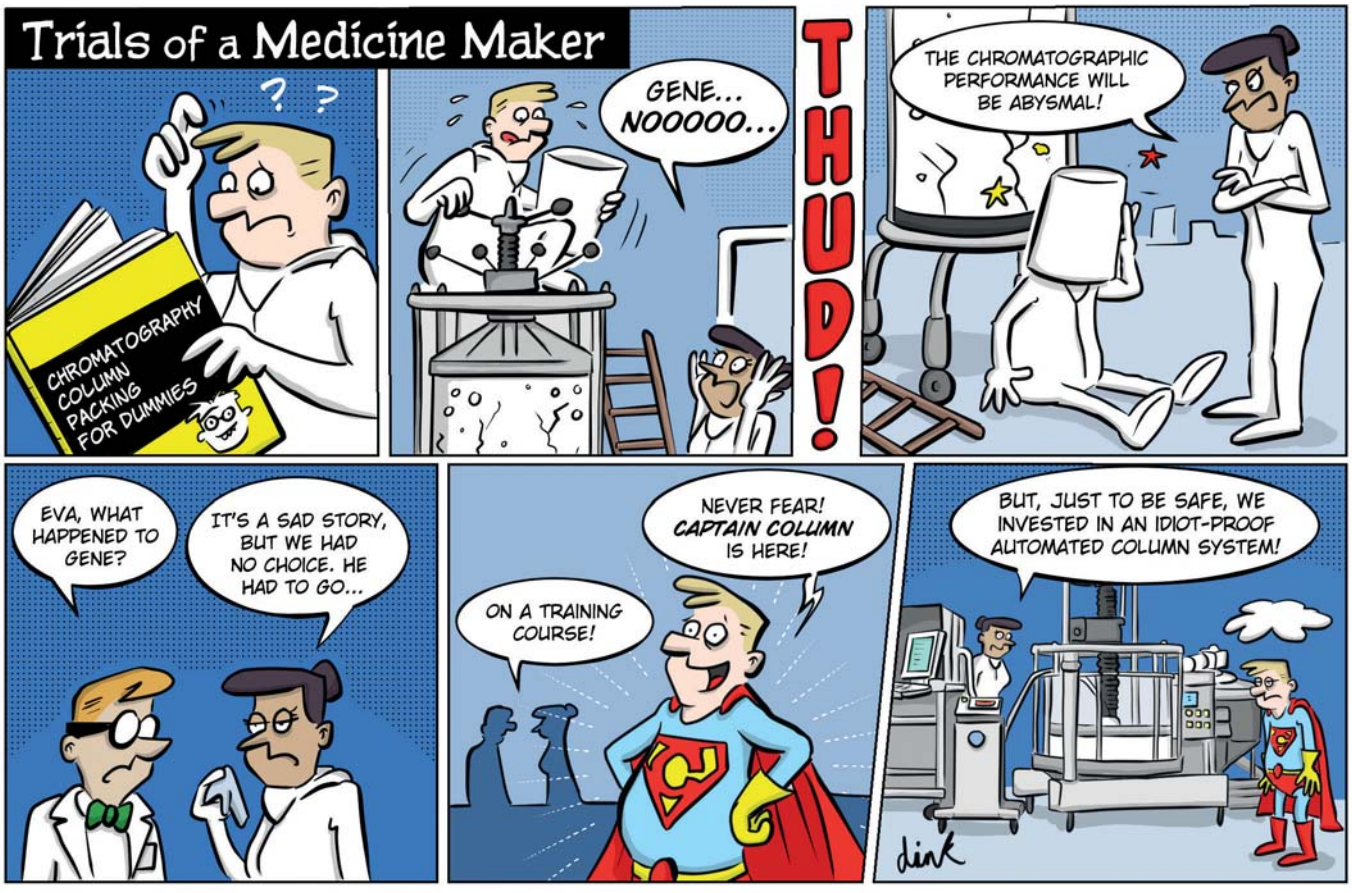
The study analysis indicated that when women are screened and enrolled in clinical trials, their percentage participation is roughly equivalent to that at the conclusion of the study. Jenkins and co-authors hypothesize that there are unknown factors in the "pre-screening" environment whereby women are not being invited or considered for clinical trial participation. "This is a gap in knowledge and an area of research needed in order to better clarify why women's participation is lower in some types of cardiovascular clinical trials," says Jenkins. "Advanced age at disease onset may contribute to under-enrollment of women. And so prevalence-adjusted representation of women in cardiovascular clinical trials across relevant age categories is also an area for future inquiry."

The FDA and its Office of Women's Health are leading a number of initiatives, with the overarching aim of encouraging the inclusion of more women in clinical trials. "In the past 20 years we have seen great improvement in women's participation in clinical trials. Since 1998, the FDA has required reporting of clinical trial data for drug approvals by gender, race and ethnicity, and age," says Jenkins. "When clinically meaningful differences between men and women are seen, these are considered as a part of how we balance risk and benefit, and how we label medicines."

Reference

1. *PE Scott et al., "Participation of Women in Clinical Trials Supporting FDA Approval of Cardiovascular Drugs," Journal of the American College of Cardiology 71, 1960–1969 (2018). PMID: 29724348*

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



Brought to you by GE Healthcare

Brexit: Preparing Is Caring

Most UK pharma companies are on track to keep their medicines on the European market by March, 2019, according to an EMA survey. But "serious concerns" remain for a significant minority

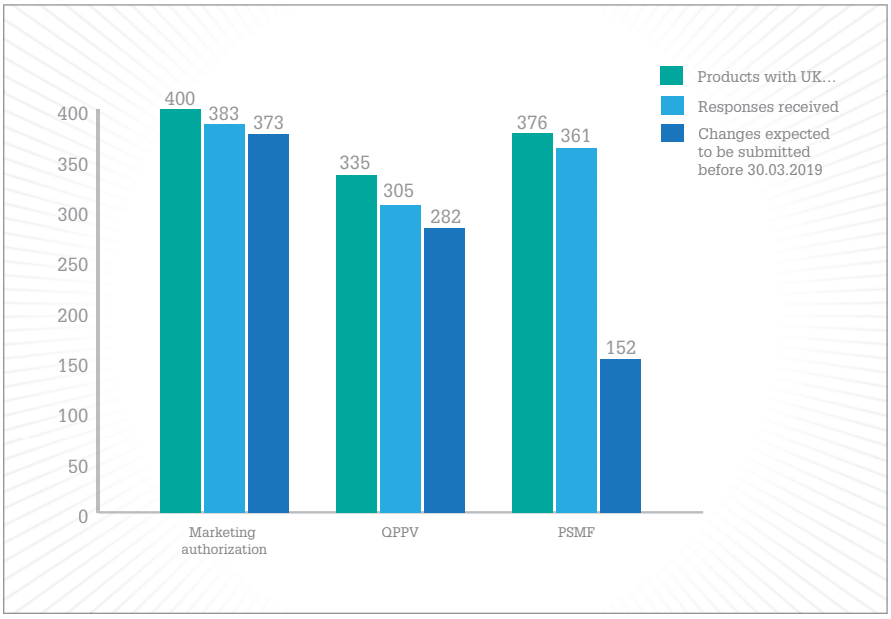
Brexit talks are at an impasse over the question of the Irish border. And unless a mutually acceptable "backstop" – to prevent the need for new infrastructure at the Irish border – can be found, there will be no Withdrawal Agreement, no transition, and no deal. As of March 30, 2019, the UK would become a "third country," where all EU primary and secondary law ceases to apply.

For marketing authorization holders (MAHs) in the UK, steps must be taken now to ensure that products can remain on the EU market after March 29. These include: transferring the marketing authorization to a MAH based in the European Economic Area (EEA), as well as changing the location of the Qualified Person for Pharmacovigilance (QPPV), pharmacovigilance system master file (PSMF), batch release, quality control and importation sites, to the EEA.

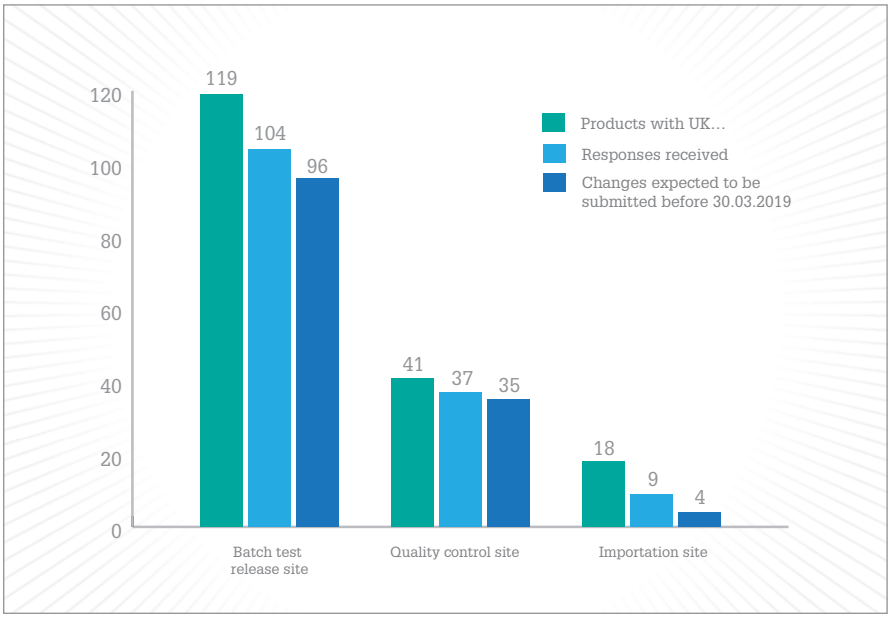
So, are companies on track? In January 2018, the EMA contacted over 180 MAHs of 694 human and veterinary centrally authorized medicinal products to find out. Their results, published in July (1), found that the majority (58 percent) of UK marketing authorization holders (MAHs) are on the ball, but there are "serious concerns" from the EMA that the necessary steps won't be taken in time for 16 percent of products.

The EMA is "strongly advising" pharma companies to submit the necessary changes for the continued maintenance of their marketing authorizations to EMA as soon as possible – at least before the end of Q4 2018.

The EMA will now follow-up directly with MAHs that do not plan to submit the changes required before March 30, 2019, to avoid potential supply disruptions.



Intention to change UK-based MAHs, QPPVs, and PSMF to EEA location.



Intention to change batch test release, quality control and importation sites to EEA location.

Reference

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MAICing a Decision

Do methods that compare newly approved drugs with those already on the market help cut healthcare costs?

Regulatory approval is seen as a major milestone in drug development, but it's far from being the final hurdle. After approval, companies must demonstrate the clinical and economic value of their product relative to other existing drugs on the market – so healthcare payers know which drugs to pay for, and how much. A lack of direct comparisons forces analysts to compare results across different studies – often with different study designs and different patient characteristics. And the problem can be especially tricky given that access to the complete patient-level data is usually only available for one study.

With these difficulties in mind, researchers came up with a new method in 2010: matching adjusted indirect comparison (1). MAIC allows researchers to reweight observations or adjust final analyses so that the patient characteristics match the summaries of another trial. In the UK, MAIC has been used in over 20 successful drug reimbursement evaluations and included in methodological guidance for indirect comparisons issued by the National Institute of Clinical Excellence (NICE).

David Cheng, postdoctoral researcher at Harvard's T.H. Chan School of Public Health is co-author of a new study that looks at the statistical performance of MAIC (2). Here, we speak with him to find out more.

Who came up with MAIC and how does it work?

The development of MAIC was inspired by the real-world challenges faced by decision-makers who need to compare treatments in the absence of head-to-head clinical trials. James Signorovitch, managing principal at Analysis Group, first came up with the idea with colleagues in a 2010 paper published in Pharmacoeconomics. Since then, it has been increasingly applied in health economics and outcomes research studies and health technology assessments.

The method works by making use of individual patient level data (IPD) for one study and adjusting that population to match summary baseline characteristics reported from a published study. Treatment-specific outcomes can then be compared across balanced populations. The key to MAIC is that the analyst does not need access to IPD from both trials – just from one. This is a very common situation in practice, especially right after new drugs are approved and critical reimbursement decisions need to be made by payers. During these periods of time, clinical trial data for new drugs are usually available only to the pharmaceutical company and certain academic groups, and not broadly accessible. Mathematically, the method is similar to propensity score weighting, but uses a different approach to estimate the propensity score model compared to a traditional setting where IPD are available for all patients.

What inspired you to study the statistical performance of MAIC?

The original 2010 paper focused on proposing the method and providing guidance on practical considerations in applications. Few formal evaluations of the procedures have since been reported. The increasing use of the method, in our own applied research and by others, prompted more careful study to better understand under what data scenarios the approach can be expected to deliver reliable comparisons that appropriately adjust for cross-trial differences.

What were your main findings?

Our research identifies the conditions under which MAIC is valid. In particular, it shows that MAIC provides unbiased estimates of a treatment effect when patient characteristics between trials are sufficiently similar and the probability an individual is selected into one trial versus another can be adequately modeled. It also compares bias through extensive simulations to other common approaches to indirect comparisons. Finally, it justifies some approaches for quantifying the uncertainty in the estimates.

What impact could your work have?

Our work helps decision-makers understand when MAIC results are reliable and when there are challenges in the data that would produce unreliable results, such as sample sizes that are too small. And that could, in turn, enable better decision-making and ultimately inform smarter allocation of resources to drugs that work best.

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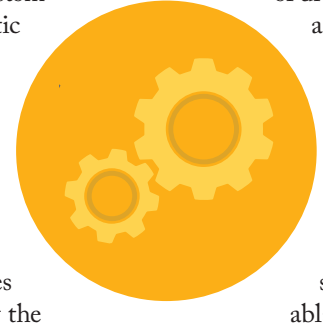
1. *JE Signorovitch, "Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept", Pharmacoeconomics, 28, 935-45 (2010). PMID: 20831302.*
2. *D Cheng, "The Statistical Performance of Matching-Adjusted Indirect Comparisons", (2018). Available at: http://bit.ly/2KyVCU0. Accessed August 8, 2018.*

The Future's RoSA

A robotic arm takes mass spec analysis of 3D objects to the next level – and could be used to probe drugs on the assembly line without destroying them

Facundo Fernandez and his team at Georgia Tech have been working on combining a robotic arm with mass spectrometry (robotic surface analysis – RoSA-MS) (1) – and it could prove a boon to pharma manufacturing. According to Fernandez, as mass spectrometers have grown more user-friendly and powerful, the bottleneck in the analytical pipeline has become the sampling process. "I feel it's time to marry advances in automation and machine learning with mass spectrometry, opening new possibilities in analytics of complex systems," he explains.

RoSA-MS uses a 3D laser scanner mounted on a robotic arm, which scans the object to be analyzed, producing a 3D representation. The user then selects points to be sampled on the surface of this representation using custom-built software. The robotic arm moves sequentially through each one of these points, "touching" the surface with a sampling probe (a spring-mounted thin needle), then placing the needle into an open sampling port that washes away material detached by the needle. The material is then dissolved and analyzed, giving the user a mass spectrum for each point.



Fernandez is confident that the robotic arm could have a range of applications, including forensics and drug screening. "In the pharma industry, it could detect substandard products in an assembly line by rapidly using the computer vision capabilities of the system to scan 3D objects (such as a tablet), and then probing its composition quickly without having to crush, dissolve, and analyze by HPLC. It could also be used to map the distribution of drugs on 3D delivery systems, and to map tissue samples. The sky is the limit!"

Now, Fernandez is working on improving the technology by arming the robots with lasers… "We would like to develop a next generation system that uses a laser ablation probe for sampling the surface, which should increase our spatial resolution and generate more detailed images," he says.

Reference

1. *Anyin Li et al., "Robotic surface analysis mass spectrometry (RoSA-MS) of three-dimensional objects", Anal Chem, 20, 3981–3986 (2018).*

Business-in-Brief

First-of-its-kind Parkinson's trial, Brexit woes, and a vaccine scandal in China… What's new for pharma in business?

Advanced medicine

- The FDA's Center for Biologics Evaluation and Research (CBER) unveiled six new draft guidance documents covering gene therapy. The guidance documents focus on i) rare disease therapies, ii) retinal disorder therapies, iii) haemophilia therapies, iv) chemistry, manufacturing and control (CMC) information, v) long-term follow-up observational studies that collect data on adverse events, and vi) retroviral vector-based therapies testing.
- Japanese scientists will use induced pluripotent stem (iPS) cells in a Parkinson's trial for the first time, following successful animal studies. In an attempt to replace the lost dopaminergic cells responsible for Parkinson's, the researchers, led by Jun Takahashi at Kyoto University's Center for iPS Cell Research and Application (CiRA), will derive dopaminergic progenitors from iPS cells and inject roughly five million of them into the forebrain. Sumitomo Dainippon Pharma hopes to manufacture and start selling cellular medicine based on the data from the clinical trials by March 2023.

Politics

- In reaction to Brexit, Sanofi will begin to increase the amount of medicine stocks held in the UK from around 10 weeks' to 14 weeks' worth, as of April 2019, based on internal assumptions of potential delays following a "no deal" scenario, according to a statement from the company. Hugo Fry, managing director of Sanofi UK, said, "Patient safety is our main priority and we have made arrangements for additional warehouse capacity in order to stockpile our products, where global supply allows, in the UK and increase UK-based resource to prepare for any changes to customs or regulatory processes."
- In the US, Senators Dick Durbin and Chuck Grassley have proposed funding-bill amendments forcing pharma companies to put drug pricing in their ads – as proposed by President Trump in his American Patients First blueprint for reducing drug prices. The proposal has bipartisan backing, including from the Democrats. PhRMA remains opposed, arguing that including list prices may deter patients from talking to a doctor about treatment.

Scandals

- The Chinese government has promised tough penalties for those involved in the sale of 252,600 faulty vaccines, after widespread public anger. A special cabinet investigation team found that Changchun Changsheng Bio-technology, the vaccine maker involved, had manufactured inferior vaccines, falsified data, sold ineffective vaccines, and fabricated production and inspection records relating to a rabies vaccine used for infants.
- A Republican congressman in the US has been charged with insider trading after allegedly telling his son the results of a clinical trial so that they could sell stock. Chris Collins was heavily invested in Innate Immunotherapeutics, a small drugmaker based in Australia. The company has no approved drugs and the failed multiple sclerosis trial sent its stock tumbling once the news went public. Federal prosecutors are accusing Collins of using his knowledge of the failed trial to sell stock before the news went public – avoiding losses of more than $570,000.

In My View

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

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

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

Designing Packaging for the Elderly

Why are we still making life difficult for a growing patient population, when solutions exist?

By Stephen Wilkins, Director, Davies Development and Testing Limited, and Chief Executive, Child-Safe Packaging Group.

Over 597 million people in the world – 8.2 percent of the population – are 65 or over (1). In the UK the proportion is 17.3 percent, and in the EU it is 18.2 percent.

Ageing is not as debilitating as it was in our parents' or grandparents' day, but it still brings with it a unique set of problems – and it is not necessary to be a student of gerontology to appreciate the impediments of age. We have known about the issues faced by the elderly for years. Shakespeare knew – consider his monologue describing the Seven Ages of Man from the play As You Like It.

For the purposes of this article, obvious impediments that come to mind are:

- Impaired eyesight. According to the Royal National Institute for the Blind (RNIB), there are 11 million people in the UK with low vision.
- Reduced manual dexterity and manual strength, including pinch strength.
- Fingertip friction rapidly degenerates after the age of 65. I often say to colleagues that if they dab their fingertips, in talc the resultant loss of friction resembles that of a 65 year old. Try it.

These are generally (or should be) easy to deal with, when it comes to medical packaging. Large clear fonts and graphics are beneficial for those with impaired vision. Large tabs on packaging like blister packs can help compensate for the loss of fingertip strength and friction. And suitable polymer specification can deal with the lack of pinch strength.

Less obvious and capable of remedy is the fear that many elderly people have of getting it wrong or looking stupid; the fear of not being able to open simple packaging, or being unable to make a supposedly simple inhaler work – never mind the more complex drug delivery systems that are also now on the market.

A lot of drug packaging is difficult for elderly people to handle or open – and it shouldn't be. Despite everything we know about the pains of the elderly, why are fonts often too small to read and tabs too short to grip? I've seen so many packaging designs for ordinary solid or liquid medicines that are just counter-intuitive, and inhaler packaging that doesn't even mention the ten priming actions necessary to actuate the pump. Packaging is a minefield that can easily destroy the confidence of the already unsure – and damage health.

Medicine packaging that is difficult to open leads to poor patient compliance. And poor compliance prolongs diseases, selects for resistant bacteria and generally drags down the health of the population. Lack of compliance also destroys brand

"Packaging is a minefield that can easily destroy the confidence of the already unsure – and damage health."

value. When medicines seem not to work, users blame those medicines rather than their own lack of compliance (and patients today are only too happy to talk about bad experiences with medicine to others and online).

Testing for ease of opening by older adults has been with us for some time. All child resistant packaging has to achieve a 90 percent success when tested by a panel of 100 adults aged 50-70 years. This is all set out in ISO 8317 (Child-resistant packaging – Requirements and testing procedures for reclosable packages) and EN14375 (Child-resistant non-reclosable packaging for pharmaceutical products. Requirements and testing) standards, to which child resistant packaging must adhere. But the panel age group of 50-70 years is unsatisfactory because it doesn't reflect the population. And standard packaging is not really tested for openability at all.

In the standards writing community, BSI, CEN and ISO, we have worked hard to create standards that can help the whole supply chain create more elderly friendly packaging. From 2005, work began in parallel between CEN in Europe and ISO in Japan. It culminated in a CEN technical specification in 2011 and finally an ISO standard: ISO 17480, Packaging – Accessible design – Ease of opening. Published in 2015, ISO 17480 is a comprehensive and helpful document that includes a panel test with a realistic sample age range of 65-80 years, taking into account user's context of use, opening strength, dexterity and cognition. It also deals with the equally important aspect of reclosing, and includes designer's and conformance checklists.

What have we failed to do thus far? Quite simply, although it has been available for more than two years there has not been adequate take-up of ISO 17480. This is despite the fact that compliance with the standard will give a competitive advantage and brand protection and maintenance in one quick step, as well as (incidentally) provide a better service and product to elderly people, who are a substantial part of pharma's customer base.

Reference

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The Great Gelatin Debate

Why we shouldn't forget gelatin's longstanding reputation as a reliable and trusted excipient.

By Bjorn Vergauwen, Principal Scientist, at Rousselot Expertise Center, Ghent, Belgium.

Gelatin has been used for decades on a large scale across many industry sectors. Owing its popularity to its multiple functionalities and nutritional profile, it has huge application potential in the manufacture of various food, nutraceutical and pharmaceutical products. However, similarly to other ingredients of animal origin, gelatin has attracted the attention of vegetarian and vegan consumers, who are increasingly demanding animal-free substitutes. As far as capsules are concerned, for example, a number of plant-based excipients are becoming available on the market for the formulation of vegan shells. Despite the initial appeal of these vegan substitutes, manufacturers argue that gelatin remains the safest, and most convenient functional ingredient with a decade long background of research and application history that no other non-animal protein can offer. Moreover, none of the vegan-friendly excipients can offer a clean label status, which represents a real challenge when it comes to meeting other consumer trends. In light of recent developments, gelatin still represents the most viable choice for capsule formulation. Allow me to explain my view.

Film and gel forming excipients are crucial in the manufacture of high quality hard and soft capsules. By "high quality," I mean the combination of optimal handling in filling machines, adequate shelf life stability and, of course, optimal in vivo performance. When it comes to excipients, the pharma industry is spoilt for choice. There's the industry standard – gelatin, which has been used for manufacturing hard and soft capsules for nearly a century. Gelatin is derived from animal sources and has

"To really understand the benefits of gelatin, the challenges of capsule formulation must first be discussed."

distinct clear label properties. There's also hydroxypropyl methylcellulose (HPMC), which works well for formulating vegan hard capsules, but isn't digestible by the body and sometimes requires a gelator (such as kappa-carrageenan or gellan) for adaptation to production process. Another hard capsule shell excipient alternative is pullulan, which is derived from fermented fungus. Like the first-generation HPMC capsules, pullulan shells also require a gelator and need a plasticizer or dissolution enhancer (such as polydextrose, mannitol or sorbitol) to avoid capsule brittleness and improve in-line capsule handling. In the face of increasing industry demands, such as rising costs and sophisticated fill formulations, I believe that gelatin is the reliable and well-established choice.

To really understand the benefits of gelatin, the challenges of capsule formulation must first be discussed. Consumers can be fickle, and they are increasingly demanding more from their capsules. For example, the trend for "all-natural" nutraceuticals is showing no signs of abating. As consumers become less interested in more "processed" products, clean label is an increasingly desirable attribute – a key driver for gelatin remaining a popular excipient choice. Gelatin is the only excipient of those mentioned above that has no e-number, and is therefore not classed as an additive, making it ideal for clean label capsules. A clean label has less effect when it comes to prescription pharmaceuticals, but consumers and patients tend to favor claims such as "free-from additives" and "natural origin."

More important than labeling is excellent technical performance. Manufacturers favor optimized bioavailability, reduced crosslinking and low oxygen permeability. Compared with other alternatives, gelatin displays outstanding immediate release dosing (1) – an important parameter for capsule-dosed medicine formulation. For alternative excipients, it is more difficult to guarantee equally fast opening times. First generation HPMC, for example, is more unpredictable in releasing APIs (2), which makes it less reliable in the formulation of prescription medicines.

With any excipient, crosslinking is always an important consideration. An excipient's crosslinking ability can negatively impact soft capsule opening time, therefore affecting bioavailability. Because of its natural amino acid composition, gelatin, in general, is more susceptible to crosslinking in the presence of complex fills, for example, but specific gelatins with reduced crosslinking ability exist. For APIs with complex stability profiles, low oxygen permeability is another important factor that must be considered when formulating capsules with the greatest performance. When the four main excipients are compared, gelatin and pullulan offer superior oxygen barriers, making them the safest choices for capsules (3).

The final challenge for capsule formulation is operational effectiveness. Machinability, cost-efficiency and weight variations are key indicators in determining the right excipient in this area. Gelatin's thermoreversible property allows a high level of machinability – meaning it can withstand an encapsulation machine and melt at body temperature without affecting its properties or functionality. For manufacturers wanting to reduce expenditure, gelatin-based capsule production outperforms alternatives in terms of cost efficiency. For instance, raw materials for HPMC capsules are priced approximately four times more than gelatin (4).

The four main excipients – gelatin, HPMC, pullulan and modified starch all have GRAS status in pharmaceutical and food applications by bodies such as the World Health Organization – and all offer unique advantages depending on your application. Some in the industry prefer plant-based excipients and are, therefore, turning away from gelatin, but gelatin really does have a longstanding heritage as a trusted, reliable and natural excipient with high effectiveness. Gelatin alternatives, on the other hand, are still in their infancy, and there currently isn't a plant-based excipient on the market which is completely natural, as cellulosics and starches need to be chemically modified to be used as capsule shell excipient.

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Perfect Process; Perfect Match

Enzyme engineering has opened up new possibilities in biocatalysis, but computational techniques and smart libraries also make wildtypes feasible. The choice is yours.

By Beatriz Domínguez and Ahir Pushpanath

Biocatalysis is an exciting, emerging technique for manufacturing APIs. Not only is it green, but it also fills in some of the gaps presented by other catalytic processes, given that it allows new transformations and routes that would not be possible with traditional techniques. Johnson Matthey has been working with catalysts for many years, so we understand the science well. Today, our portfolio of biocatalysts, advanced computational techniques for enzyme development and expertise in reaction engineering, optimization and scale up are making biocatalysis a true complementary solution for most given transformations.

It's a hit

Finding a good "hit" comes down to sampling and screening a diverse collection of enzyme sequences covering a large portion of a given enzyme family.

There is no shortage of effective enzymes that can be used for biocatalysis, but finding the right enzyme for the job, within reasonable timelines and limited resource expenditure, remains a challenge – or perhaps it's more appropriate to say that it's a "numbers game," with millions of potential combinations to investigate. We obtain our enzymes from a variety of sources, including natural enzymes from the public databases, newly discovered enzymes through metagenomic approaches and enzyme engineering. If you have a large portfolio of enzymes, known to catalyze a broad variety of different substrates, you clearly increase your chances of finding an effective hit. In short, you need the enzymes and the ability to test them rapidly – and we have both at Johnson Matthey.

But finding the hit is just the beginning because it will be based on a very small-scale reaction under diluted conditions, typically a long way off a solution that can be used industrially. However, it is still possible to improve the process. You need to be an expert on reaction engineering and you need to understand how to modify the set ups to achieve the full potential of the catalyst. The first task is to find out where the limitation lies: is it the catalyst or the process?

Generally, we find that, when you move to very concentrated conditions, the enzyme will be limited in terms of its stability (thermo or organic stability, for example). The rate of the enzyme itself could also be inhibited in high substrate loadings. Such limitations can be overcome with reaction engineering, but you can also use enzyme engineering. This is only becoming more popular as our understanding of enzyme structure-function relationships grow, together with the tools to build rational design libraries. We use highly advanced computational techniques that enable us to study the 3D model of each enzyme and rationally select specific regions of the sequence that require fine tuning through mutagenesis.

Through these *in silico* approaches, we can usually identify a suitable mutant within two months. For enzyme engineering to be streamlined, however, you need to have a clear goal in mind and this involves in-depth discussions with our clients.

The natural way

Where possible, we try to develop biocatalysts that do not require enzyme engineering at all – it is possible, and tends to be faster and cheaper. If you screen a large and diverse enough sampling of enzymes – and our collections are large enough to do this – you may find that some are promising enough to work at an industrial level without the need for enzyme engineering. Additional enzyme engineering may not be suitable for every client depending on their timelines and available resources – and if something exists in nature then why not use it? It's very important to communicate and collaborate with clients to develop the best solution. Sometimes clients come to us and say they need enzyme engineering, but, based on our in-depth knowledge, we may be able to offer another solution that could work better for them.

"Newly discovered enzymes are continually being added to our portfolio."

When building our portfolio, we have focused on creating a broad toolbox of potential solutions. Newly discovered enzymes are continually being added to our portfolio as new research is performed. One area of interest is in the synthesis of chiral amines due to their commonality in pharmaceuticals. Traditionally, chiral amines are developed using transaminases, which is offered by many biocatalysis companies. We are also looking at other enzymes classes that will allow for the transformation of pro-chiral ketones to chiral amines: amine dehydrogenases and imine reductases. Both are attracting considerable attention in the research community because of their efficiencies as biocatalysts.

Beatriz Domínguez is R&D Manager and Ahir Pushpanath is Team Leader, Biocatalysis, both at Johnson Matthey, UK.

STANDING UP FOR THE INVISIBLE MANUFACTURERS

Despite the increasingly essential role of CDMOs in the pharma and biopharma industry, their collective viewpoints and challenges have been overlooked once too often. Such organizations were in serious need of a voice – and so the Pharma & Biopharma Outsourcing Association (PBOA) was born.

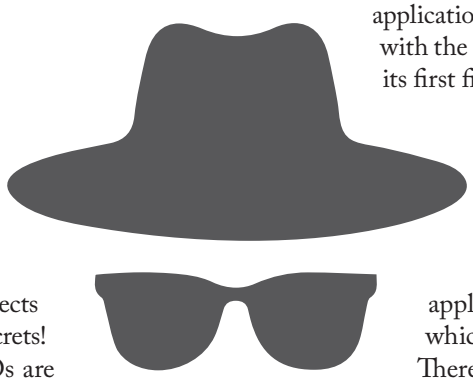
As told by Gil Roth

Contract manufacturers are unsung heroes. They produce medicines to the same quality standards as pharma companies and comply with the same regulations, but they do not receive the same profits as their pharma counterparts, nor recognition by patients. Their name does not go on the label of the medicines they help develop, and regulators and legislators have tended to overlook the outsourcing sector when making crucial decisions. The issue was highlighted in 2013, with the introduction of Generic Drug User Fee Amendments (GDUFA). These user fees, negotiated by the FDA, the generic industry and several other industry groups, were structured in a way that unintentionally created a large fee burden on contract manufacturing facilities in the generics space. When the sector started to receive invoices from FDA, they wondered why they were bearing this burden when they hadn't been invited to the negotiating table.

The reaction? The birth of the PBOA. Without an association, things like GDUFA could come up again and, to quote an adage from a senator of Louisiana, "If you're not at the table you're probably on the menu…"

"GDUFA wasn't designed to be malicious against CDMOs – those at the table simply didn't realize how CDMOs would be affected by regulation X or legislation Y."

WHO ARE YOU?



It's difficult to obtain transparency and exact figures about how involved CDMOs are in the pharma industry. Even if you know a facility is making drug X, you won't know the volumes – and CDMOs and clients treat their projects and partners as heavily guarded trade secrets! According to PBOA's estimates, CDMOs are involved in around 30 to 40 percent of the drugs made for the US market, but the figure could be higher.

My first encounter with contract manufacturing was back in 1999 when I became the founding editor of an industry magazine called Contract Pharma. In time, I built up a good knowledge and appreciation of the sector, as well as very good relationships with many CDMOs. I started reporting on GDUFA in 2013.

The background to GDUFA is that the volume of Abbreviated New Drug Applications (ANDAs) for generic drugs was increasing and the generic industry wanted the FDA to review these more quickly and work through the extensive backlog of ANDA submissions. Between 2007 and 2011, it was taking the FDA 18 to 30 months to approve an ANDA. There were also delays in foreign inspections. The FDA was keen to accelerate access to generic medicines for patients, but couldn't expedite the review process without additional funding for more staff and modernized IT systems. Enter generic drug user fees to allow the FDA to build a program to review applications more quickly and effectively, and cope with the challenges of globalization. GDUFA I, as its first five-year authorization period was known, generally mirrored the Prescription Drug User Fee Act (user fees for innovator drugs; introduced in 1992), but where PDUFA had establishment fees that were assigned to the NDA/BLA filers, GDUFA's facility fees were applied directly to "manufacturing sites" – which meant that CDMOs had to pay out. There were also no reductions or fee waivers for small companies.

User fees are important for the sustainability of the review process, but GDUFA I caused CDMOs many problems. For example, if a facility's first ANDA was delayed, then CDMOs would end up paying fees – potentially for years – before receiving payment for manufacturing services. CDMOs with multiple sites were hit hard, and some sites were receiving multiple sets of fees because they handled both APIs and finished dosage forms (FDFs). There were also instances of CDMOs receiving bills because out-of-date ANDAs listed their manufacturing sites or ANDA filers listed a CDMO's site

without consulting with the CDMO.

The impact of those FDF facility fees was a case of unintended consequences; GDUFA wasn't designed to be malicious against CDMOs – those at the table simply didn't realize how CDMOs would be affected by regulation X or legislation Y because the outsourcing sector did not have representation during negotiations in 2012. A few CDMOs tried to get involved in the negotiating process but were told by the FDA: no trade association, no representation (understandably so, as the FDA would be swamped if they started letting individual companies in).

Once I reported on the impact of the first year of FDF facility fees on CDMOs, I felt very strongly that we needed to do something, so I asked people in the industry if they thought we needed a trade association. The general response was yes – and that I should quit my job at the magazine and run it! I laughed at the time, but soon after the president of one CDMO approached me. He'd been talking with executives at other companies about the need for a trade association, and pushed me to talk with other CDMOs too. At the Contract Pharma annual conference in 2013, I put together a symposium of 30 to 40 representatives from CDMOs. We discussed what the sector wanted and needed from a trade association, and how attendees thought it should be structured and funded. There was a lot of interest, but less idea of what form it would take.

At the time, I didn't think I was going to leave my job to take the task on, but over the next couple of months, as people kept asking, "What's next?", I realized a trade association was never going to materialize unless someone took the lead. I began reaching out more seriously to companies to ask them three basic questions: Do you really believe we need a trade association? Do you really believe I could run it? Would your company put up X amount of dollars as seed money as a founding member? I received a resounding "Yes!" to all three questions from the first five companies that I called. And so I quit my job to launch a trade association.

GETTING TO THE TABLE

Progress was fast. Within a week, I'd put together marketing materials, set up meetings, and walked into the Waldorf-Astoria for meetings at DCAT. With a new trade organization, you might have expected it to be a struggle to recruit members, but within two months 15 member companies had signed up. We incorporated PBOA as a non-profit, established a board of trustees drawn from a dozen founder-level companies, and were up and running by the middle of 2014. We held our first board meeting at BIO that year. The goal was clear: to

WE ALL STAND TOGETHER

The founding companies of PBOA from 2014:

Sustaining Members

Afton Scientific
Baxter Biopharma Solutions
Coldstream Labs
Cook Pharmica
Gallus Biopharmaceuticals
Halo Pharma
Hospira One2One
Jubilant HollisterStier
Metrics Contract Services
Patheon
Therapure Biomanufacturing
WellSpring Contract Services

General Members

Coating Place, Inc.
DPT/Confab
AAI/CML (now Alcami)

Bringing competitor companies together is always a challenge, and it's also a challenge to unite companies that perceive themselves as being very different – why should a biopharma CDMO stand with a small-molecule focused CDMO? Ultimately, what dosage form a CDMO is making is less relevant than the fact that they all revolve around providing services. PBOA encourages members to recognize each other as peers. Not all of PBOA's focus areas will apply to every member (we have a few members who weren't subject to GDUFA fees at all and we also have a Canadian Affairs Working Group for the 10 member companies that have operations in Canada), but it's important to recognize that there now exists an association that represents the group as a whole. Through PBOA, CDMOs are taking responsibility for their place in industry. If a member raises something that they feel needs to be discussed – even if it doesn't apply to every member company – it will gain our attention.

ISSUES THAT MATTER

PBOA has a number of working groups, but it all began with quality metrics. During an FDA public meeting on quality metrics, I asked some questions about the agency's initial draft guidance during the open comments section. A few of our members were in the audience and afterwards another trade group came by to ask how they could get us involved in their cross-industry group on quality metrics. I told them I would speak with our Quality Technical Group – and then sat down with the members who were in attendance and asked if they would be the core members of our new Quality Technical Group. The group worked with the cross-industry group for a response on the draft guidance, and opted to meet monthly via a conference call to discuss topics coming down the pipe in terms of FDA regulatory dockets, as well as to share questions based on experiences from inspectors and other regulators. They now help members with data integrity questions and promote the sharing of best practices while continuing to address guidances on the FDA's docket.

We liked the way the Quality Technical Group got our members talking – and I considered it a key success of PBOA. From there, we added a Serialization Working Group, an Over-The-Counter Monograph Group (Congress is currently looking at this space to introduce a new user fee that would primarily be levied on manufacturing facilities), and a Canadian Affairs Working group. We also have an Opioids Working Group. Congress has worked on a number of proposals in the US for dealing with the opioid epidemic, and we want to make sure that our members are providing feedback.

One of our newest working groups focuses on drug shortages – an issue that we've been concerned with since PBOA's inception, and which came into prominence after Hurricane Maria struck in September 2017. Scott Gottlieb tweeted about how FDA is working night and day to help alleviate drug shortages resulting from the disaster in Puerto Rico, which affected many manufacturing plants. I tweeted back that PBOA's members were ready to help in any way they could to help maintain the supply of critical drugs. A day later, FDA's Incident Management Group contacted me to ask how our members had been impacted by the disaster.

Supply chains can be very complex and my members' responses surprised me. I was thinking primarily of companies that operated sites in Puerto Rico, but it turned out some received bioprocessing components from the island and didn't know if there were secondary sites. Others manufactured product that was shipped to Puerto Rico for the customer, where it was then packaged and sent out globally. We started working with the FDA to fill in the blanks in terms of supply chain, as well as helping companies, such as Patheon, that had facilities in Puerto Rico affected by the storm. From there, we began working on proposal how CDMOs can help when manufacturing site problems lead to drug shortages. The Drug Shortage Working Group has developed a number of interesting ideas on this topic, a sign of the importance of PBOA's Working Groups.

"To be taken seriously, we had to be up to speed on everything the FDA needed for GDUFA, while making sure that we were protecting the interests of the CMO sector."

get a seat at the table when GDUFA came up for reauthorization (FDA user fees come up for reauthorization every five years) so that we could negotiate a fee model that offered a more level playing field and was fairer to CDMOs.

One of PBOA's first challenges was to convince the FDA that we were a legitimate stakeholder who should be included in the GDUFA II negotiations. Initially, the FDA seemed a bit unsure about bringing in another trade group. Three trade groups were involved for the first GDUFA, and all were returning for GDUFA II. The FDA didn't know our sector or how we were different to other interest groups (which underlines how much a trade association was needed). To be taken seriously, we had to be up to speed on many of the policy and implementation issues related to GDUFA I, while making sure that we were protecting the interests of the CDMO sector.

In March 2015, we invited a key FDA policy maker for GDUFA to speak to our members at our Regulatory Workshop in Washington, DC, explain how GDUFA was performing, and to listen to our questions and complaints in terms of the fee structure. A few months later, that policy maker called and agreed that we were an important stakeholder and needed to be involved in the upcoming negotiations.

The actual negotiating period covered 10 months from the fall of 2015 to the summer of 2016. During that time, we tried to make sure that the agreement – and not just the fee structure – would suit both large CDMOs and small CDMOs. In fact, our core negotiating team included two of our largest member companies along with our smallest – to ensure that all voices were heard.

Our efforts paid off. When GDUFA II was signed into law on August 18, 2017, it featured reduced FDF facility fees overall, with a further reduction for CDMO facilities and an exemption for sites that were still waiting for their first approved ANDA. Under GDUFA II, CDMOs now pay one-third the annual FDF facility fee paid by firms that manufacture under ANDAs owned by themselves or their affiliates.

ANDA		$171,823
Program	Large	$1,590,792
	Medium	$636,317
	Small	$159,079
DMF		$47,829
Facility	Domestic API	$45,367
	Foreign API	$60,367
	Domestic FDF	$211,087
	Foreign FDF	$226,087
	Domestic CMO	$70,362
	Foreign CMO	$85,362

Fees under GDUFA II for 2018.

The achievement was proof of concept that PBOA worked and had a strong voice that could impact regulation and legislation. A number of new members joined us after that result. Today, we have 35 member companies (no mean feat given the M&A activity in the sector these past few years). We also have affiliate members, which are companies that provide goods or services, such as marketing, serialization software, and lyophilization equipment, to our members. And we've developed a number of working groups where member companies can focus in on key topics (see sidebar, Issues That Matter).

FACING CONGRESS

The issues with GDUFA I stemmed from the fact that regulators and legislators did not understand the pharma outsourcing sector. Through the process of negotiating GDUFA II, PBOA built relationships with the FDA, not just with the office of generic drugs, but with other departments and offices; awareness of what we do – and the importance of CDMOs – is proliferating to other important offices of the agency. After the GDUFA II negotiations concluded, the FDA contacted us about serialization because the deadlines were approaching and they hadn't heard directly from CDMOs about their progress. We also had other meetings at the agency, including a sit-down with CDER Director Janet Woodcock and her team to talk about the CDMO sector and what we do, how we can work better with the FDA to help them to better understand new manufacturing technologies, and the role we can play in helping to alleviate drug shortages.

When we first incorporated PBOA, I expected to be dealing solely with the FDA, but I soon learned that once an agreement like GDUFA is made, it is forwarded to Congress, where it is packaged with other bills, voted on, amended, and so on, before ultimately being signed into law by the President. In addition, a lot of FDA initiatives, like serialization/track & trace, originate with Congress. That meant we couldn't stop at the FDA. We had to begin lobbying Congress to educate them about our sector and to ensure that no one changed the fee model or introduced an "improvement" in GDUFA that would accidentally hurt CDMOs.

This means I had to register as a lobbyist (not something I ever thought would happen, back when I was editing a trade magazine). We also retain an advocacy firm in Washington, DC that helps set up meetings and represents us at Capitol Hill (because outsourcing is good!). Our firm informs us about topics that are coming down the pipe – and there is a lot going on in Congress, especially nowadays, that impacts the overall healthcare sector. Raising the profile of CDMOs has given us the opportunity to meet with the congressional offices, explain

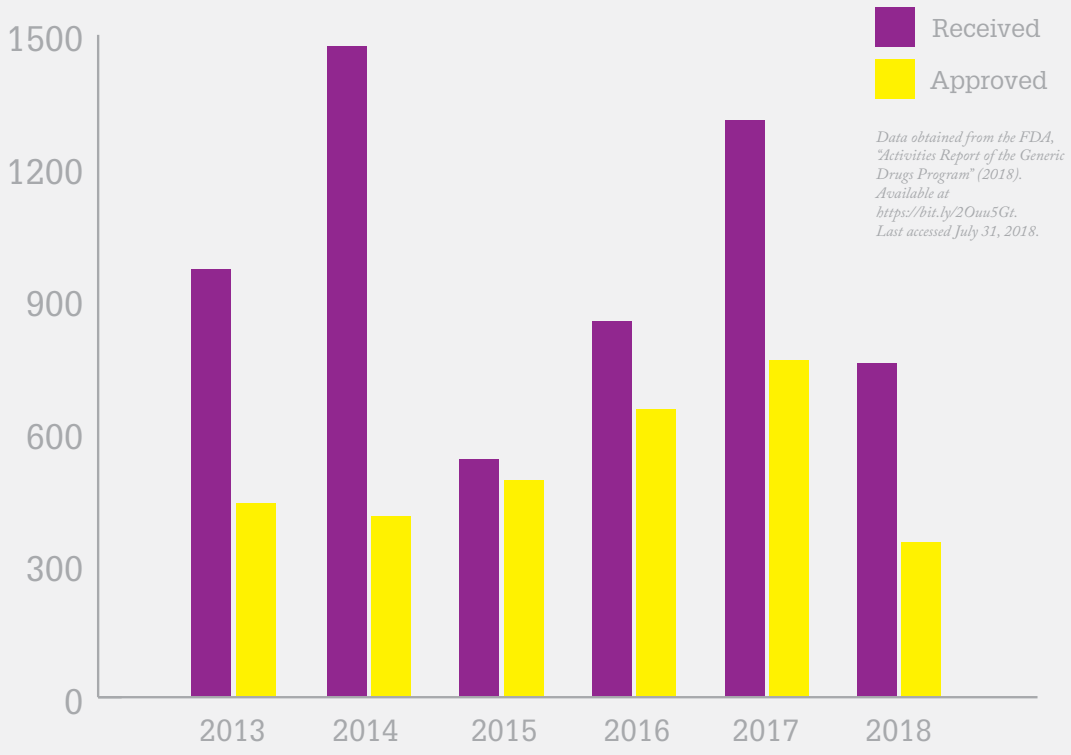
GDUFA II – KEY POINTS

- Facility Fees for Finished Dosage Form (FDF) and API sites account for a smaller portion of GDUFA's overall collections.
- There are three tiers for the new annual program fee – based on the number of approved ANDAs owned by a firm (20 or more = large; 6 to 19 = medium; 5 or less = small).
- No facility fees for sites identified only in pending submissions; fees are triggered when a site is reference in an approved ANDA.
- No fee for prior approval supplements.
- CDMO FDF facilities will pay one-third of what a non-CDMO FDF facility pays in fees.
- Facilities manufacturing both APIs and finished dosage forms will only pay one fee.
- No CDMO tier for API manufacturing facilities.
- If an ANDA submission is withdrawn before received for filing, the company can apply for a 75 percent refund.

Fees under GDUFA I in 2017:

- Domestic FDF facility: $258,646
- Foreign FDF facility: $273,646
- Domestic API facility: $44,234
- Foreign API facility: $59,234
- Total GDUFA budget: $323,011,000

Figure 1: Abbreviated New Drug Applications at the FDA.



the role that CDMOs play, and their economic importance – not just in terms of healthcare, but also in job creation in particular districts and states – and how our members empower biotech startups via development services. Once people understood that CDMOs are a critical (but previously unseen) part of the healthcare ecosystem, they began reaching out to PBOA proactively on new issues and ideas developed by other industry groups to gauge their impact on our members.

I've said a lot about FDA and the US Congress, and PBOA is a US-based association, so I am often asked about our relevance to CDMOs outside of the US. Pharma and biopharma is a globalized industry, and if you manufacture for the US market – the biggest pharma market in the world – then, as far as the FDA is concerned, their rules and standards affect you! They will come to inspect you and they will bill you with any relevant user fees. And that means PBOA is the only association that represents you as a CDMO.

We are also expanding our reach – we're building bridges with Canada's regulator, as new regulations about foreign facilities could impact the CDMO sector. We're also talking with a Japanese CDMO association about their needs and interests to see how they dovetail with ours. In time, we'll look at what we can do in Europe. It's so important to get our members comfortable with talking to regulators. Regulators are people and they really like to know what's going on in the industry. I've been pleasantly surprised at how interested they are in learning about both the CDMO and business perspectives. They need to know how we differ from pharma companies, even though we are all held to the same quality standards.

PBOA started in 2014 because of GDUFA, but I'm amazed at how far we've come and how many other areas of interest we have as an industry. Today we are keeping an eye on many topics from NAFTA (North American Free Trade Agreement), China tariffs and Brexit – which will be very important for our members who sell into the UK and the rest of continental Europe – as well as serialization, opioids, OTC monograph reform, and many others. Drug pricing is another key topic, both on a federal level and within individual states around the country. As talk of new

legislation arises, we need to make sure there is an understanding of the difference between pharma companies and CDMOs. If legislation is proposed that says the "drug manufacturer" has to provide X, Y and Z, for example, we would ask for it to be amended to focus on license-holders for drugs, and exempt companies that just perform contract manufacturing. (It is my private mission to get people to differentiate between the license-holder of a drug and the actual manufacturer: a Quixotic quest, at times.)

RESPECT

It's been almost 20 years since I got involved in the sector, and four and a half years since we launched PBOA. During my career, I think clients have garnered a much greater understanding of the importance of CDMOs. Many major pharma companies have drastically re-shaped their supply networks in the last couple of decades and now see their CDMOs as partners (although the definition of "partner" varies wildly). There are many start-ups out there too who are dependent on CDMOs – their own development and commercialization efforts would be so much tougher and require immensely more capital without the availability of contract manufacturers and their development services. At the same time, there is always a need to propagate standardized best practices in terms of how clients and CDMOs work together. There are countless stories from CDMOs about insane client demands – and I'm sure clients have their own frustrations with CDMOs!

I believe CDMOs should be treated with respect, from regulators, legislators, and their customers. It is easy for some people in the industry to dismiss them as service providers, but CDMOs have a huge wealth of manufacturing expertise, are often early adopters of new technology, and are, frankly, indispensable for many pharma and bio companies out there. The collective expertise of PBOA members is outstanding. CDMOs are involved in countless projects and they have seen it all: different drugs, different customers, and different regions. I think it's fair to say that our members have been exposed to a far wider variety of projects than an in-house pharma site and so they have a great deal to contribute to regulations, legislation, and quality manfacturing.

At industry events, you'll often find CDMOs standing at booths selling services or waiting for meetings. Rarely are they guests – and even rarer is the conference built specifically for them. PBOA has started running a conference that puts them in the spotlight. I think it shows that we are trying to advance the outsourcing sector – CDMOs are not just sitting idly by, selling services and waiting for things to come down the pipeline; they are discussing the future and how they can prepare for it. We held our first PBOA members conference in October 2017 and the next one will be in September 2018. Along with numerous industry experts, we had five FDA speakers at the 2017 event, covering quality metrics, serialization, mutual recognition of inspections with EMA, inspection trends, and the overhaul of the FDA inspectorate and how it will impact CDMOs. We've become a focal point for the FDA to reach out to.

For me personally, it has been a huge learning curve. We have done so much already – but there is still plenty to do. It emphasizes how much a trade association was needed for the sector. We can't just negotiate one user fee and walk away – we need to make sure that we are invited to the table in the future and have continuity with the FDA and with our industry partners. Every morning I read the Federal Register updates to identify regulations and executive orders that may affect CDMOs (dull reading, but very important!), while our advocacy firm in Washington keeps me apprised of legislative proposals. I send out newsletters to keep our members up to date with what's going on. We also have monthly legislative update calls for our members, and our working groups meet regularly by teleconference so that members can both learn what's going on in their areas of interest and relate their experiences. (This has been facilitated by recently bringing aboard Chris Verbicky, one of our first trustees, as PBOA's Director of Scientific and Regulatory Affairs.)

PBOA exists to make sure that everyone understands the importance of CDMOs, and we will continue to raise the profile of pharma and biopharma outsourcing. We will make sure our unsung heroes are never overlooked again.

Just Can't Get the Staff!

Or can you…? The second article in our Biopharma Trends series explores staff development in the industry: which positions are hardest to fill? What skills are most in demand? And what can companies do to ensure they discover and nurture talent?

By James Strachan

With many of the first generation of bioproduction staff reaching retirement age, along with an increasing number of biomanufacturing facilities coming on line, finding the right staff can be a real challenge for the biopharma sector. But help is at hand. In the second article of our Biopharma Trends series (see sidebar), we explore what a recent survey conducted by The Medicine Maker and Ireland's National Institute for Bioprocessing Research and Training (NIBRT) reveals about staff development in the biopharma sector (1).

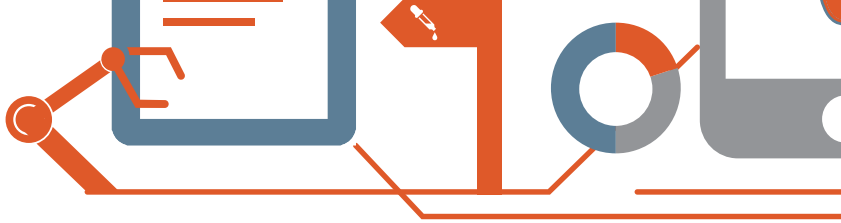
Here, we will reveal respondents' thoughts on which positions are difficult to fill and why, what skills companies are looking for, and how can we best equip the biopharma professions of the future. To analyze the results, we've enlisted the help of our survey collaborators, Ireland's National Institute for Bioprocessing Research and Training (NIBRT) – and their Director of Projects, Killian O'Driscoll – as well as experts from Thomas Jefferson University (Ron Kander and Kathleen Gallagher), and the International Society for Pharmaceutical Engineering (ISPE; Jeffery Odum and Andre Walker).

Bioprocess engineers in demand

The results of our survey showed that a majority (86 percent) of survey respondents had difficulty filling one or more biopharma positions (Figure 1). Bioprocess engineers were the most difficult position to fill (52 percent), followed by manufacturing science and technology staff (39 percent), upstream processing staff (33 percent), and downstream processing staff (28 percent).

"This largely aligns with our experience," says O'Driscoll. "In particular, what we see is a shortage of what you might call engineers with 'specialist skills' – not just bioprocess engineers, but automation engineers, commissioning, qualification and validation engineers, and so on. It's really a question of supply and demand." O'Driscoll argues that the biopharma industry is growing rapidly and that such roles are in especially high demand for start-up organizations. "It takes four to five years to train a bioprocess engineer, with perhaps some post-graduate study, and ideally a few years' experience as well," he says.

Ron Kander, PhD, (Dean, Kanbar College of Design,



"In the US, there are too many competing opportunities for the skill sets identified."

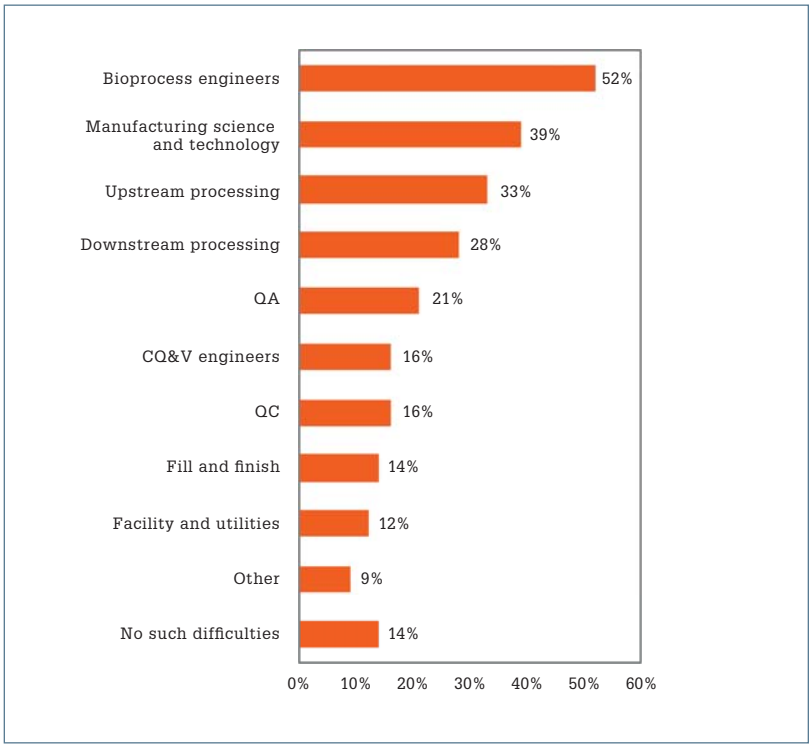
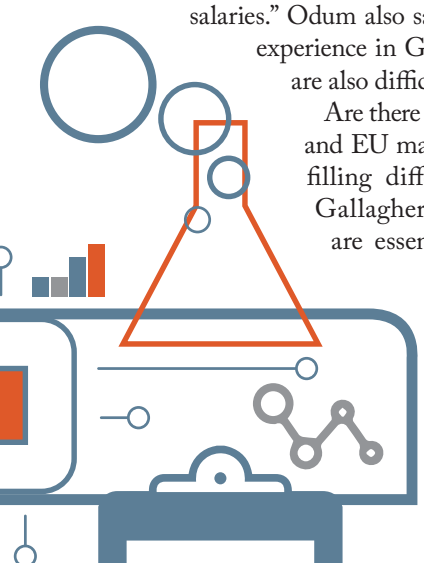


Figure 1. Which of the following types of staff were respondents having the most difficulty hiring? (Survey respondents were allowed to choose more than one response to this question; hence why the responses total more than 100 percent.)

Engineering & Commerce, and Associate Provost for Applied Research) and Kathleen Gallagher (University Executive Vice Present and Chief Operating Officer), both from Thomas Jefferson University, concur. "Bioprocess engineers and biomanufacturing specialists are in short supply because there are very few facilities like the Jefferson Institute for Bioprocessing (JIB) and NIBRT that combine hands-on training on industry-scale equipment with an industry-validated curriculum," says Kander.

Jefferson Institute for Bioprocessing was the first major program to emerge from the merger between Thomas Jefferson University and Philadelphia University. Jefferson partnered with NIBRT to deliver NIBRT's curriculum to its students – you can read more about it here: http://tmm.txp.to/0318/training. "When we speak with industry professionals, they tend to cite a lack of trained professionals in bioprocess-related support roles – including supply chain, regulation, purchasing and sales/marketing – who understand and appreciate bioprocessing unit operations," says Gallagher.

Jeffery Odum, Global Technology Partner in Strategic Manufacturing at NNE and Teaching Fellow at North Carolina State University's BTEC, and ISPE member, offers that universities contribute to the shortage of process engineers. "Most university programs do not teach or promote the discipline focused in the life science in a way that attracts students," he says. "Another problem is that other industries are recruiting from the same talent pool – and they often offer higher starting salaries." Odum also says that project managers with experience in GMP-focused project execution are also difficult to hire and retain.



Are there any differences between the US and EU market with regard to difficulties filling different positions? Kander and Gallagher believe the two markets are essentially the same. "Most large multinational corporations and small toll manufacturers are working in a global marketplace," Kander notes. "This is one reason we are partnering with NIBRT – so someone trained at JIB or NIBRT will have equivalent experiences and will also allow workers to move seamlessly between positions in North American and Europe, making them more valuable to their employers."

O'Driscoll agrees that there are similarities between the two markets, given that there are global trends in play. But he does see some potential differences emerging, with US companies perhaps more focused on discovery. "As we look at the newer modalities – cell and gene therapies, for example – coming through," he says, "we may see an emerging lack of skills there, particularly in the US marketplace because of their strong emphasis on discovery."

Odum believes the EU has done a better job promoting this GMP-focused industry as a whole, "this has generated more interest," he says. "In the US, there are too many competing opportunities for the skill sets identified."

Can't beat technical skills

In addition to the most difficult positions to fill, we also asked respondents to rank the importance of different skill

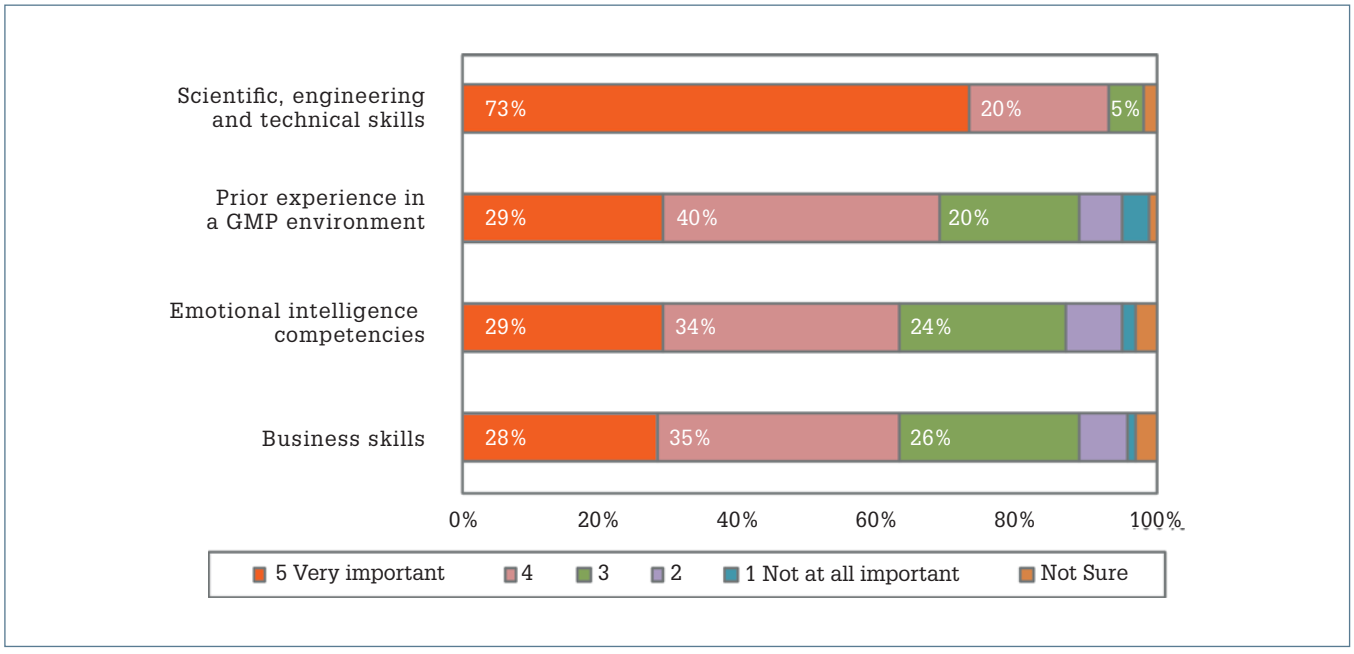


Figure 2. With regard to hiring new staff, how important is each of the following skill sets?

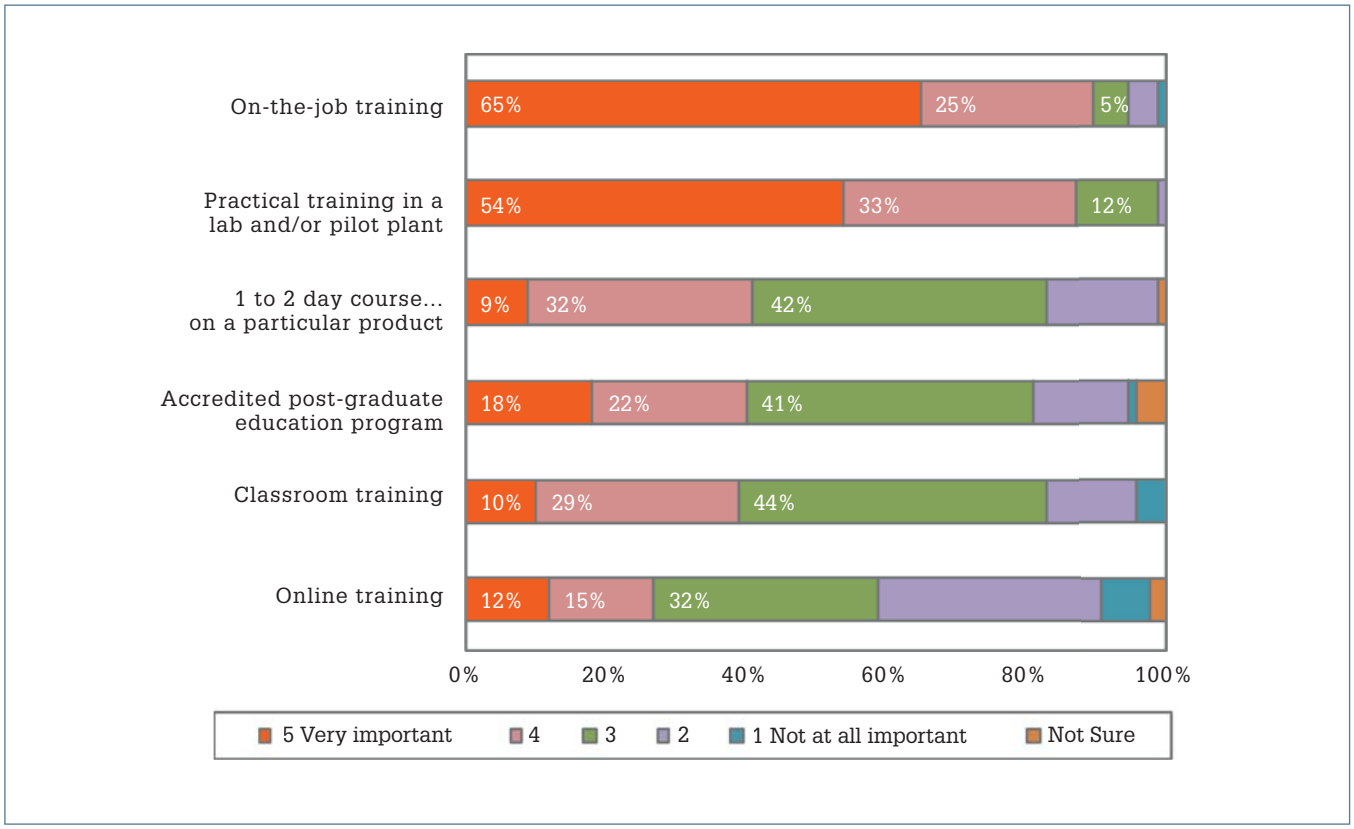


Figure 3. How effective are various types of training? (Using a scale of 1 to 5, with 1 being not at all effective, and 5 being very effective.)

How to find the right people

Andre Walker: Leverage networks by incentivizing existing employees to bring in known acquaintances, and then regularly publicize specific job openings to staff so they are prompted to consider their network against the opportunity. Promote from within and fill the bottom with recent graduates who are supported by well-designed training and mentoring programs.

Killian O'Driscoll: We see companies succeeding when they adopt a multi-faceted approach – underpinned by developing a strong brand, based around their employee culture. We see some startups having great success, sometimes recruiting up to 400 positions for new manufacturing facilities, when they do this. As well as using the traditional route of hiring, consider engaging with local schools, offering internships to university students, engaging at the apprentice level, and cross-skilling existing staff – perhaps from other disciplines such as small molecule manufacturing. Companies must also support continuous professional development and lifelong learning for those hired.

Jeffery Odum: Seek to collaborate with an institution that is open to innovative partnerships. These types of models have proven very successful at the community college level.

Ron Kander and Kathleen Gallagher: It is cheaper to grow talent internally and train existing employees than it is to recruit people away from your competition. Companies want to partner with the Jefferson Institute for Bioprocessing (JIB) to co-develop internal training programs for existing employees, and are also interested in identifying talent early in the academic process to "lock in" future employees by offering named scholarships, internships and graduate fellowships to students in our undergraduate and graduate Bioprocess Engineering programs. Companies are also working with our regional community colleges to identify high-quality technicians they can hire and then complete a bachelor's or master's degrees in the JIB facility while they are working. All these strategies are centered on identifying, retaining and growing talent from within the organization.

sets (Figure 2). The most important skill set for new hires was scientific, engineering, and technical skills (rated as 4 or 5 by 93 percent of survey respondents). Whereas the remaining skill sets were each considered quite important by 63 percent to 69 percent of the respondents. The results also indicated that individuals in small companies were more likely to consider scientific, engineering and technical skills; prior experience in a GMP environment; and emotional intelligence competencies as being quite important, while those working in large companies were more likely to consider business skills, such as communication or team work to be quite important.

"Of course practical skills are vital for a career in the biopharma industry," says O'Driscoll. "But we've seen a change over the past five-or-so years. Previously, when companies were hiring, they were looking for a very specific skillset for particular roles. What we're now seeing is that as skills evolve and change and new types of roles emerge, the attitude of the person you're hiring is fundamental."

O'Driscoll also points out that EU GMP Guidelines (annex 1) talks about the importance of skills training and attitudes (2). "What a lot of companies are realizing is that you can hire for attitudes and then train for skills. Hiring managers will ask: can they work in teams, problem solve, conform to advanced manufacturing regulatory requirements, and learn on an ongoing basis – with a fundamental focus on quality and the patient?" He believes that the perfect hire will be someone with those softer skills and the scientific, engineering, and technical skills. "Clearly that would be the ideal situation, but those people are in short supply. Companies will therefore take into consideration attitudes and realize that people can acquire skills through continual professional development," explains O'Driscoll.

Andre Walker, consultant and ISPE member, says the kinds of skills required depends on the position. "If you are hiring for a technical position then scientific, engineering, and technical are very important skills," he says. "But in my experience, biopharma companies, easily attract the most technically qualified candidates, so the key skills that result in a job offer are soft skills such as leadership, communication, and teamwork."

Odum agrees, adding, "It's amazing to see how the art of communication is being lost in the age of Facebook and instant messenger."

Kander and Gallagher, however, say that employers are more interested in hands-on, practical training with real equipment. "This can range from in-depth technical training for technicians and engineers who are running bioprocessing facilities to hands-on technical awareness training for people in support roles such as sales, marketing, purchasing, legal

and supply chain," says Kander. "Employees in the biopharma industry must understand the science and engineering behind the bioprocessing unit operations and also understand in detail the operation of each step in the process.

"Another key skillset is the overall operation planning and control functions needed to successfully operate an integrated biomanufacturing process," Kander adds. "Finally, one must understand how the biomanufacturing process interfaces with the rest of the business operation, including R&D, sales, purchasing, supply chain, regulation and legal."

> "If you are hiring for a technical position then scientific, engineering, and technical are very important skills"

On-the-job does the trick

Respondents were also asked to rate the effectiveness of various types of training (Figure 3). On-the-job training came out on top (rated as 4 or 5, with 5 being "very effective") by 90 percent of survey respondents), closely followed by practical training in a pilot lab and/or pilot plant environment (87 percent). Several other types of training were considered less effective: a one- or two-day course from a third-party provider on a particular topic (41 percent), an accredited post-graduate education program from a higher level education institute; for example, a Master's in science program (40 percent), or classroom training (39 percent). The least effective type of training was online training, which was rated as quite effective by only 27 percent of the respondents; though individuals located in Asia were more likely to consider online training to be quite effective, compared to those in Europe or North America.

To Walker, these findings make sense. "Correct GMP behavior comes mostly from modeling other's actions in everyday work and interacting with specific quality systems that are similar but not identical to other organizations," he says. "For operational roles (operator, warehouse, etc.), SOP's codify the actions required, but are rarely useful as day-to-day instructions. After classroom training on the requirements correct performance is achieved through documented practice and repetition with appropriate oversight." For engineering and technical support roles, Walker believes general knowledge

Biopharma Trends Trio

In December last year, The Medicine Maker teamed up with NIBRT to find out about current trends in the biopharma industry. We asked 210 biopharma professionals from across the world a series of questions covering: product pipelines, manufacturing practices, staff development, opportunities and challenges within the sector. Fifty-seven percent of the respondents worked in biopharma manufacturing, 13 percent as contract service providers and 13 percent in companies that were suppliers/vendors to biopharma companies. The remaining 17 percent were affiliated with academic institutions, government organizations, or consulting.

The first article in the series looked at biopharma therapeutics, now and in the future (read it at https://bit.ly/2vi5jRZ). Respondents rated mAbs as the most commercially important biotherapeutic right now, but saw cell and gene therapies as being very promising for the future. We also spoke to four Power Listers about their thoughts on the survey results and their advice on what biopharma needs to focus on to rise to the challenges that lay ahead for the field.

The third and final article in this Biopharma Trends series will consider the future of the biopharmaceutical manufacturing and gather opinions on Industry 4.0 – the fourth industrial revolution.

"Most universities are aware of what industry needs; they're flexible, they're responsive."

from university studies and the review of specific corporate procedures provide explicit (well documented) knowledge of a field, "but this is only the foundation upon which tacit (tribal, experiential, practical) knowledge is gained," he says.

"On-the-job and practical training is more effective because of the hands-on, experiential aspect of these pedagogies," say Kander and Gallagher. "This approach ensures that students and industry trainees will be able to retain the complex information associated with bioprocessing unit operations. There is no substitute for training on real bioprocessing equipment."

Is there more universities could be doing to prepare students for careers in the biopharma industry, given the importance of on-the-job practical training? "Yes, if they are willing to spend the money and collaborate with industry," says Odum. "But the traditional tenured academic research-driven platform does not lend itself to OTJ-type models."

O'Driscoll thinks that universities should be given credit for what they've done to date in supporting and driving the biotech industry from its origins over 30 years ago. "But for sure the industry is changing rapidly," he says. "Most universities are aware of what industry needs; they're flexible, they're responsive, while still making sure that they are teaching the core skills and competencies that are required for graduates – but there's always room for continuous improvement. That's why we're delighted to see what Jefferson are doing in the US and we're aware of similar initiatives throughout the globe."

Look out for our third and final article in this Biopharma Trends series, where we look at the future of the industry and opinions on Industry 4.0. Industry 4.0 represents the adoption of intelligent, data-driven approaches, and is already bringing tangible benefits to other sectors. But which elements can benefit biopharmaceutical manufacturing.

Industry 4.0 will also be explored at an upcoming conference to be held in Cork, Ireland, 13-14 November 2018. Find out more at: www.biopharmatrends.com.

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Meet the Experts

Killian O'Driscoll is Director of Projects at NIBRT and has been involved in the successful establishment of the Institute, which has numerous international accolades including ISPE Facility of The Year and Bioprocess International Manufacturing Collaboration of the Decade. He is also Associate Lecturer in Project Management at Dublin Business School.

Jeffery Odum has over 25 years of management experience in the design, construction, and commissioning of facilities in the biotechnology and pharmaceutical industries. Jeffery served as the North American Education Advisor to ISPE and is co-Chair of the ISPE Biotechnology Community of Practice. He has led training efforts in fifteen countries, including training for global regulators from the US FDA, Health Canada, and the Chinese SFDA.

Andre Walker is a consultant with over 30 years of experience providing engineering and technical support for manufacturers of biopharmaceuticals, medical devices, and consumer products, including 13 years in Director roles for Biogen with postings in the US and Europe. Andre has served as the Chair of the ISPE International Board of Directors in 2011 and is currently the Chairman of the upcoming BioManufacturing Conference.

Kathleen Gallagher is University Executive Vice Present and Chief Operating Officer, at Thomas Jefferson University, where she leads the operation and administrative aspects at the multiple university campuses, including the university's campus integration and strategic planning efforts.

Ron Kander, is Dean of the Kanbar College of Design, Engineering and Commerce and Associate Provost for Applied Research at Thomas Jefferson University, USA. He teaches and does research in the areas of materials selection and design, systems dynamics modeling, complex data visualization, and integrative design thinking.

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Getting to Grips With the New Generation

How will biopharmaceutical process development be affected by next-generation technologies?

By Herb Lutz and Brian Hubbard

There are a number of different ways of describing next generation bioprocessing, including continuous manufacturing and intensified processing. Next generation bioprocessing covers a variety of different techniques, from combining process steps, to moving from batch to perfusion bioreactors, to new cycling operations – but all are ultimately designed to deliver significant improvements in manufacturing costs, speed, efficiency or flexibility. Some descriptions of particular technologies are laid out in the BioPhorum Operations Group's (BPOG) Biomanufacturing Technology Roadmap (1). Next generation processing technologies and techniques do not just offer incremental improvements. If we have a 14-inch and a 12-inch filter, the development of an 8-inch filter would not be considered "next generation," for example. A membrane adsorber though that can be run at shorter residence times and cycle rapidly to reduce a column size from tens of liters to just one liter would hit the mark. The reduction in size would also make the use of single-use technologies viable, and with single use, you can also start to think about fully closed systems for better bioburden control, among other benefits.

As next generation processing is new for biopharma, a perfectly human response is to be wary. One of the key comments we hear all of the time is that "regulators will never allow this". That is not true. If you listen to regulatory presentations, they often talk about next generation technology to improve the quality of medicines and to make medicines more available (2). Regulators are very open to discussing technologies with companies as a means of encouraging adoption. The FDA has an Emerging Technology Program, the EMA an Innovation Task Force and in Japan the PDMA Innovative Manufacturing Technology Working Group allows manufacturers to obtain early regulatory input on different types of technologies and how to validate them (3).

Risk assessment is a useful tool to identify, prioritize, and start to address uncertainties. Gap assessment is another tool to identify needed data or analysis to reduce uncertainty. One of the most effective ways of managing risks with new technology is gradual adoption, such as rolling out hybrid processes that combine batch and intensified processing. Gradual adoption allows manufacturers to trial and select the processes that have the best benefits for the molecule or the facility in question.

The move to continuous is a natural evolution for a manufacturing industry. Processes typically start out as a batch process because in a batch process it is easy to manage risk. The process steps are uncoupled from each other so if one step goes down, the remaining steps can still proceed. There is slack time and intermediate inventory built in to the batch process to allow response to upsets. As experience is built and process steps become more reliable, you start to think about connecting steps and reducing costly inventories and poor process utilization. Many other industries have now done this. In the early days of biopharma, contamination in the bioreactor was common, but now we can go years without seeing an incident. Why? Because we have more experience. And I believe that we now not only have the experience, but also new technologies like single use, to maintain sterility and allow us to connect steps without significantly increasing overall process downtime.

Process planning

The potential benefits of implementing next generation technologies lie in reduced capital costs, manufacturing flexibility, plant efficiency and speed to market, but there have been many

questions raised in the industry about how process development will also be affected and what problems manufacturers might encounter. It's important to remember that the quality attributes associated with the molecule will be the same regardless of how the drug is produced. However, there will be some changes in process attributes and their relative importance. There is more emphasis on risk for a next generation approach because it is continuous. The stopping points in a batch process provide ample opportunity for recovery from an upset, but if there is a problem in a continuous line then you need to divert the intermediate product to waste, which is expensive. Process monitoring and control is critical to identify upsets and respond quickly to avoid compromising final product quality. Once a process is up and running, however, automation makes the process easier-to-run, with fewer deviations and risk, than batch processes.

Broadly speaking, next generation bioprocessing is not fundamentally very different to traditional batch processing. You'll be running some of the filtration steps at constant flow instead of constant pressure, cycling faster with shorter residence times, and be running in flow-through mode rather than bind-elute mode, but for the most part the physics underlying how each step works are the same. For example, adsorption is based on charge and is the same whether done with a membrane or a resin – and still the same if you cycle faster in a next gen approach. The shorter residence times, however, mean that the target operating point moves in your design space.

Of course, there are some steps that will be very different, such as perfusion, which has the new operating parameter of turnover in the bioreactor. If you have a 200 liter perfusion bioreactor, you need to consider how many liters equivalent you are then feeding and withdrawing every day. If you have 200 liters of media that you're adding and 200 liters of product that you're removing, you'll have a turnover of one volume per day. With perfusion, there is also a perceived risk by some in the industry that the quality of the drug product in perfusion will be worse than in fed batch. Cells will be producing in perfusion runs that may last for weeks – and I've heard concerns raised that the quality of the drug product may degrade over time. Bear in mind, however, that drugs most sensitive to degradation, e.g., Factor VIII, cannot be processed in fed batch and are produced in perfusion because perfusion has higher yields with less product degradation!

Changing from a batch low pH virus inactivation process to an inline continuous process involves replacing multiple mixing and holding tanks with pipe inactivation chambers. This reduces footprint, the complexity of managing multiple Protein A elutions in multiple tanks, and improves the uniformity of the inactivation solution. Residence times in the inactivation chambers are potentially shorter than with conventional batch operation. The product protein will sit in acid for much less time, meaning lower protein degradation, higher quality and better yields. We're also able to control the flow and so forth in this incubation chamber much better than in a 2000 liter tank, so it's much better for monitoring and controlling the process. Informal discussions with health authorities and biomanufacturers show a lot of interest in this work.

One significant difference between batch and next gen is the processing time. In batch, a product spends around two weeks in the bioreactor and then moves downstream, where it is processed by successive steps for a few hours each day. In a next generation process, product quickly moves out of the bioreactor and through the downstream steps in hours. Less residence time means less potential for degradation. This process can continue for perfusion production campaigns that can run 14-90 days. The campaign is typically broken up into smaller lots lasting just a few days, and while this increases the lot release testing costs, it also reduces the risk of an upset, causing one to have to dispose of the entire campaign. Within a lot, many operations will be performed in a cycling manner to reduce their size and cost. It is possible to size steps so that, at the end of a lot, adsorbers may have cycled through their active life and can be disposed of. The entire wetted path can be replaced with no carryover between lots.

Next generation processing is new, so of course there will be many questions and in time we will resolve these. As one example, I've heard many discussions about batch definition, but remember that there is actually flexibility with how a lot is defined so a manufacturer can choose how a lot is defined in continuous – perhaps by certain volumes, or volume turnover of the bioreactor, or days, or mass. It just has to be clearly defined prior to manufacture. Despite the questions and the industry's fear of change, a lot of people are very excited by next generation processing.

The topics raised in this article were discussed in more detail in a recent webinar we gave. You can watch the recorded webinar at your convenience at: www.merckmillipore.com /nextgenseries.

Herb Lutz is Global Principal Consultant, MSAT, at Merck, and Brian Hubbard is CEO of CMC Bioprocess Consulting LLC. The life science business of Merck operates as MilliporeSigma in the US and Canada.

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Bringing Alzheimer's in from the Cold

With big pharma seemingly pulling out of the field, what hope remains for novel treatments for Alzheimer's disease? Here, we gain insight from a small but pioneering company and researchers in the Alzheimer's research space to discover that – with the support of the wider community – there are significant reasons to be hopeful.

By Roisin McGuigan

You'd be forgiven for thinking that the pharma industry has completely abandoned Alzheimer's disease (AD) research. At the start of 2018, Pfizer made the decision to terminate its neuroscience discovery programs, leading to a significant backlash in the media with dramatic (and negative) headlines lamenting big pharma's exit from the field. Over the past few years, numerous pharma companies have seen failures of once promising Alzheimer's drugs in their pipelines, and there hasn't been a new drug approved for AD in over a decade.

Is there truly no hope left? Pfizer's announcement in January wasn't all doom and gloom – the company added that it would be creating a venture fund to invest in biotech companies conducting promising neuroscience research. And research in both company pipelines and academia continues. Here, I speak with some of the people refusing to give up on Alzheimer's.

Untangling Alzheimer's

By Claude Wischik

There is no getting around the fact that developing treatments for AD is difficult. The disease is characterized by the development of two distinct pathologies in the brain:

- Senile plaques composed of β-amyloid located predominantly between neuronal cells that accumulate in normal aging without dementia.
- Tangles arising from tau aggregation, which forms small toxic pathological oligomers and then filaments within neuronal cells. These aggregates are highly correlated both with clinical dementia and with imaging abnormalities commonly used for diagnosis.

We still know surprisingly little about what triggers the aggregation of these proteins, but we do know that the process starts decades before any clinical symptoms of dementia appear. There is also little understanding of how abnormal processing of the proteins that give rise to β-amyloid plaques and tangles are linked, and which comes first. There are robust associations between clinical decline and the largely homogenous spread of the tangle pathology throughout the brain. It has been known for some time that the association between clinical decline and β-amyloid pathology is much weaker than for the tau aggregation pathology. This has been confirmed in recent years using specific ligands that permit the two forms of pathology to be visualized in living patients using PET imaging.

The only real success to date has been with the development of symptomatic treatments that modify cholinergic and glutamatergic neurotransmitter activity. But the last new approved treatment for AD was 15 years ago, so there has been a major failure in the field to develop fundamentally novel approaches, despite the pressing socio-economic need. Symptomatic treatments provide only modest and temporary relief from ongoing clinical decline in cognition and global functioning. Their widespread availability may also be creating problems for the development of novel approaches – because symptomatic treatments have become the "standard of care," it is difficult to conduct clinical trials of drugs except as add-ons to these treatments. Moreover, the chronic brain stimulation produced by these drugs may actually interfere with the action of drugs that address the underlying pathology or other novel symptomatic treatments.

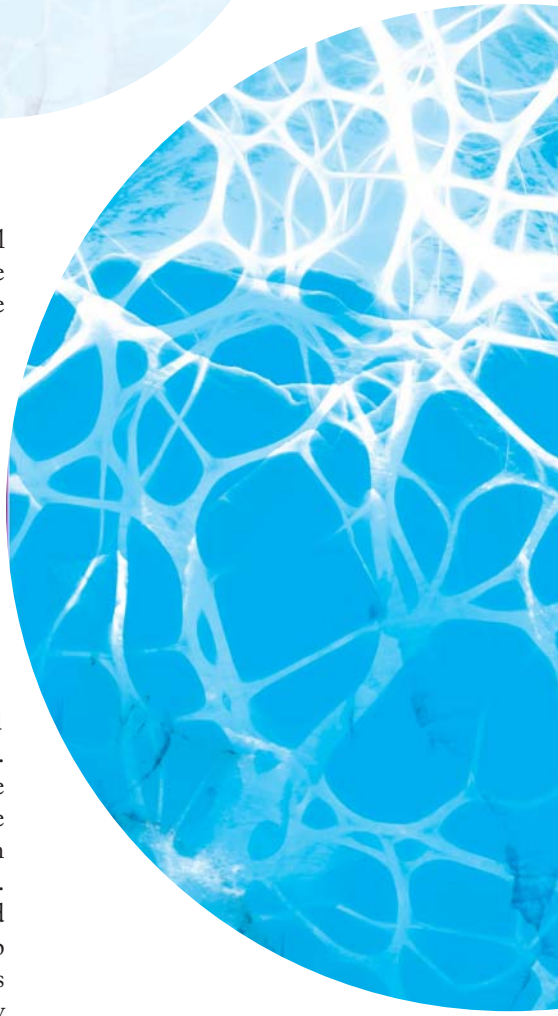
A further factor that makes the development of treatments difficult is the nature of the decline that patients undergo, which is slow and variable – whether treated or untreated with currently available drugs. Clinical trials need to be large and long, even if the treatment effect is small.

In my view, treatments that prevent the spread of tau aggregation pathology offer a very attractive avenue of attack. It is now known that the spread is mediated via prion-like processing that converts tau protein into an infectious particle – one that resists proteases and is able to seed further tau aggregation in previously healthy neurons.

A disease of the future

As human lifespans increase and the world's population ages, the incidence

"Symptomatic treatments provide only modest and temporary relief from ongoing clinical decline in cognition and global functioning."



of AD is predicted to reach epidemic proportions. It is estimated that there are 47 million people currently living with AD, and that this figure will increase to 75 million by 2030 and to 132 million by 2050. If left unchecked, this disease has the capability not only to devastate the lives of patients, families and caregivers but also to have a major financial impact on public healthcare systems across the world. As both a doctor and the co-founder of a company, I believe that any research that contributes to the understanding of AD is vital and should be continued.

Though news headlines tend to be dominated by the failures of large-scale clinical trials to achieve their primary endpoints, even failed studies generate useful data that offer new insights into disease pathology, biomarkers and clinical progression. The AD research community has more useful data – and more sophisticated data analysis tools – than ever before. And from the point of view of market opportunity, the scale of the problem to be solved only increases.

Nevertheless, the field remains challenging, for large and small companies alike. Larger companies benefit from access to greater resources and a more focused effort on research programs and clinical trials. On the down side, the corporate decision-making that deploys large clinical trial resources is understandably cautious and must find its bearings with reference to prevailing scientific opinion. If prevailing opinion happens to be on the wrong track then large corporations can lose their way. The discovery in the 1990s of mutations in the amyloid precursor protein (APP) gene led to an almost universal adoption of the amyloid cascade hypothesis as being the prime driver of AD. New product development in multiple companies has, therefore, been focused on agents able to clear β-amyloid plaques and prevent ongoing formation. There have been promising results in the laboratory and in animal models, but the positive effect on pathology has not been reflected in clinical symptoms in humans. Though I believe that the detection and tracking of β-amyloid plaque build-up may be useful for diagnostic purposes, this pathway seems to represent an inherently inefficient approach to the treatment of the disease.

Fortunately, other therapeutic approaches are under investigation. Smaller companies are more nimble than larger entities and many are focusing on impressive science. Such companies are less reliant on prevailing opinion and able to take scientific risk. Small companies (including my own), however, are faced with the problem of the cost and resource effort required to undertake large global clinical trials. The key underlying challenge lies in Phase III clinical trial design and the unavoidable heterogeneity of the AD patient population. In around 99 percent of cases, AD is diagnosed in septuagenarians, at which time a number of other co-morbidities are likely to be present. The costs and risks associated with undertaking large-scale clinical studies in this population are significant, particularly if the drugs involved have modest treatment effects.

Hope remains

The number of products in clinical development that target the tau tangle pathway has increased markedly in the past two years, reflecting the fact that the research community is embracing this potentially more effective approach to treating the disease.

With greater collaboration and open-mindedness to novel research – and with greater investor focus on this area of medicine – we will go further, faster. If the research community had supported the tau-tangle approach and other avenues for fighting AD in the 1990s rather than simply focusing on the amyloid hypothesis, would we be looking at a very different world today?

Claude Wischik is Co-Founder and Executive Chairman at TauRx Pharmaceuticals.

The Research Conundrums

By Dennis Selkoe

The big question facing AD research today: what explains the failure of numerous clinical trials? In my view, the greatest challenge for both researchers and companies working on AD is testing subjects with experimental therapeutics prior to or near the time of onset of their amnestic and cognitive symptoms. What the numerous failed Phase II and III AD trials have in common is that they attempted to treat subjects with mild-to-moderate symptomatic AD. In some cases, the agents themselves were weak, toxic or otherwise flawed (e.g., R-flurbiprofen, tramiposate, solanezumab and semagacestat), but these and other agents were also administered too late in the degenerative process. Like atherosclerotic cardiovascular disease, AD is a chronic, slowly progressive disorder in which potential disease-modifying agents largely need to be administered prior to onset of symptoms. The other great challenge now is the need to have the first drug achieve FDA/EMA approval so that a second agent can be tested with it to move toward combination therapy, as is usually required for other chronic diseases.

Another frustrating setback has been the failure of certain agents because their trials included some (or many) patients who did not actually have AD – amyloid PET imaging was available, but not used in several of the trials to screen and select the right patients.

These challenges and disappointments have led some companies to decide to withdraw entirely from clinical research on AD and other neurodegenerative diseases. Fortunately, other companies are pushing ahead. We owe it to the world's AD patients and society as a whole not to give up, but to instead put more resources and good ideas into AD preclinical and clinical research. This added support is now coming from both biopharmaceutical companies and from the US National Institutes of Health, AD-directed foundations and major philanthropists. The costs are high, but once a single successful agent is found, it will pry open the floodgates for much greater investment in AD translational research.

I'm excited about agents coming through pipelines that efficiently target soluble Aβ oligomers (oAβ) in the brain, because a great deal of preclinical evidence suggests they are the principal pathogenic moiety that initiates the neurodegenerative process. Some of the monoclonal antibodies now in trials can bind and clear these diffusible oligomeric species (e.g., Biogen's aducanumab and Roche's crenezumab, among others), and that is encouraging. I am also excited about the advent of tau immunotherapy (vaccines and monoclonals). As tau accumulates prior to symptoms but after oAβ, combining an Aβ -lowering agent with an anti-tau agent is an attractive idea.

Delving deeper into the mechanisms of microglial alteration in late-onset AD is also important, although I think specific compounds that safely modify this ubiquitous feature of the AD cascade are not yet near.

Learning from failure

For companies that feel AD research is not viable, at present there are still contributions to be made – particularly with the vigorous sharing of natural history data and any other archived data, such as those from failed trials. Placing all clinical trial results that are not intended for an NDA or BLA into a shared public database will allow pooling of data-rich archives and improve statistical power in natural history studies and help us understand the details of progression from placebo cohorts. Companies not currently working on specific AD therapeutics should also be encouraged to contribute financially and scientifically to the global effort to advance translational research on AD by supporting public-private consortiums and AD-oriented philanthropy.

"We owe it to the world's AD patients and society as a whole not to give up."

Despite what the headlines might say about the current state of AD research, I don't think AD patients have been abandoned by any means – there are a lot of good preclinical and clinical studies underway or being contemplated. And one success will encourage those who've left the field because of the challenges to reassess and possibly return. It is unfortunate but understandable when companies choose to focus on other therapeutic areas after pipeline failures. But we must remember that there are specific reasons why AD clinical trials have not seen success so far. To cite some examples, semagacestat (a putative γ-secretase inhibitor from Eli Lilly) had a half maximal inhibitory concentration (IC50) for Notch processing that was about the same as its IC50 for amyloid precursor protein cleavage (i.e., a low therapeutic index), thus leading to significant adverse events from inhibiting signaling by Notch – and probably that of other normal substrates. Solanezumab showed a small (~15 percent) slowing of cognitive decline, but its predilection for binding Aβ monomers (not implicated in AD cytotoxicity) over Aβ oligomers made it unlikely to yield a significant clinical signal. Pfizer's bapineuzumab was a potent anti-oAβ antibody, but its induction of amyloid-related imaging abnormalities

A Charitable View

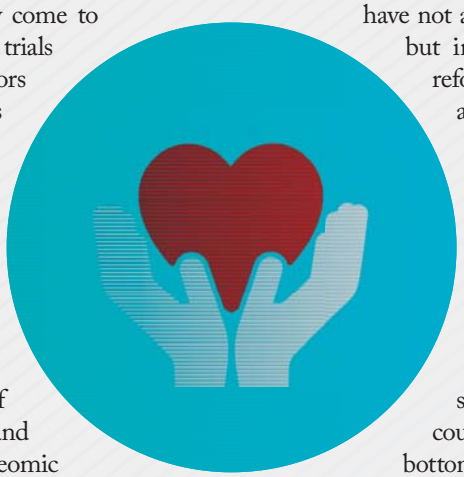
With John Davis, Chief Scientific Officer of the Alzheimer's Research UK Oxford Drug Discovery Institute.

On the institute

The Alzheimer's Research UK Oxford Drug Discovery Institute (ARUK-ODDI) was created with funding from Alzheimer's Research UK, and is one of three drug discovery institutes sponsored by the charity. We are located at the University of Oxford and focus on novel targets for treating dementia. We are lucky to not only have staff who are dedicated to finding new ways to treat neurodegenerative diseases; we are also surrounded by academic scientists passionate about their research and applying it to the fight.

On the challenge of AD

Developing drugs in such a disease area is complex and painstaking. Originally, familial genetics and histopathology identified some key targets, and these avenues have finally come to fruition in the recent trials of secretase inhibitors and antibodies targeting species of beta-amyloid. A particularly exciting recent development has been the advent of the omics era, which has enabled the profiling of genetic risk factors and transcriptional, proteomic and metabolomic changes. The linking of changes in the immune system with AD will certainly spawn a series of approaches to be tested as treatments. It's important to remember that every experiment we perform, no matter how successful or unsuccessful the result, both educates us and raises further questions. The trials using anti-beta-amyloid antibodies have produced results that have been less efficacious than hoped for, but we have learned a lot about the heterogeneity of AD patients – as well as the importance of considering at what point in the course of a disease to treat with a particular type of drug.



On support from pharma

The whole landscape for drug discovery is changing – and not just in the central nervous system space. Pharma companies engaged in drug development for many different diseases are realizing that it may be better to concentrate on clinical development and allow smaller, nimbler and more focused biotech teams to concentrate on the discovery phase. Hence, some pharma companies that may appear to have withdrawn from discovery for AD have not abandoned the field, but instead have simply refocused, and are still active in clinical development.

Projects require different types of support at different phases and pharma companies are already incredibly supportive. Of course, there is never a bottomless pit of resources, and pharma has chosen priorities that may not align with any given academic research group's specific interest. However, significant progress has been made and there are now many different public and private funding models available to an academic with a well-defined plan. One area where pharma could further help groups like the ARUK-ODDI is in the sharing of assay methodology that is not necessarily of critical proprietary value, or making compound collections available via open access, or at least with as much freedom to operate as possible.

Another current issue is that research groups and pharma generate large amounts of valuable data that reaches a limited audience, or is leveraged minimally. Publication via journals is a system that provides valuable quality control and organized publishing, but is otherwise an outmoded route of communication. More "open access" sharing of resources and data would both minimize time delays due to publication procedures or contract negotiations, and also reach many more researchers. The coordinated placing of appropriately validated methods and data onto public portals would help accelerate research.

On the future path of AD research

Despite disappointing recent trial results, increased awareness, increased funding and new technologies have produced an encouraging landscape for future drug discovery for AD. We must keep up the momentum and continually remind ourselves that the treatment of dementia represents one of the world's largest medical needs – and deserves very considerable investment in time, resources, and sweat.

with edema (ARIA-E) was a first for the field and forced the antibody to be dosed too low and ultimately abandoned. Interestingly, aducanumab has moved forward despite some occurrence of ARIA-E because the field has come to realize that the latter is a sign of moving amyloid out of the brain.

In short, more rigorous preclinical testing in iPSC-derived human neurons and in two or more rodent models of AD is needed to obtain a robust initial dossier before advancing an agent into clinical trials. The "doom and gloom" about the failure of AD trials needs to be assessed scientifically, not emotionally – there are specific reasons for the failures, and we all need to learn from those lessons.

Dennis Selkoe is Coates Professor of Neurology at Brigham and Women's Hospital and Harvard Medical School, and former chair of the external neuroscience advisory board for Pfizer.

Nanoformulations: Reach for the (Micro)Sun!

The UK's Centre for Process Innovation targets easier manufacturing of nanoformulated medicines.

By James Strachan

The market for nanoformulated medicines is growing at a significant rate – with an expected value of $350.8 billion by 2025 (1). There is also an abundance of research taking place in the field. Nanomedicines refer to cargos of therapeutics at the nanoscale and may exist as nanoparticles, nanocrystals or other formulations. Manufacturing nanomedicines – and deciding on the best delivery method – is challenging because of the very thing that makes them special: their nanosize. Indeed, significant issues with reproducibility plague nanomedicines, and there have been high failure rates in translating nanomedicines from the bench to the clinic. Today, a growing focus on microfluidics looks to provide enhanced process control and predictability.

Here, we speak with Caroline Kelly, Technology and Innovation Officer at the UK's Centre for Process Innovation (CPI), to find out how microfluidics and improved process control can give a boost to the future of nanomedicines.

Why has CPI chosen to focus on nanomedicines – and what is "Microsun"?

One important overarching topic at CPI is nanoformulations – and that's become an even hotter topic given the pharma industry's interest in nanomedicines. In one nanomaterial project, our scientists are evaluating a new microfluidic-based platform for the scale-up, process development and manufacture of nanoformulated medicines. The aim is to make the platform available for further collaborative R&D or private projects at the CPI's National Formulation Centre in Sedgefield, County Durham, UK. The project's name is Microsun.

Who is involved in the project?

The project builds upon expertise and resources currently available within the University of Strathclyde (through Yvonne Perrie) and the University of Manchester (Jayne Lawrence), who have experience in the design of nanoformulations based on lipids and polymers, respectively. We're also working with AstraZeneca, Pfizer, Croda, Malvern PANalytical, and Precision Nanosystems – whose industry experience and opinions on gaps and hurdles in the field has been invaluable.

Two work-streams will initially run simultaneously across the two universities to evaluate at-line process analytics, in-line tangential flow filtration and determine relevance to the control of product quality. At CPI, we'll be focusing on supporting the technology transfer of formulation compositions, process design, scale-up and the development of process metrologies to enhance process control.

Why are microfluidics important for the development of nanoformulations?

Microfluidics help manipulate nanoliter volumes in fluidic channels, making them essential for the scale-up, process development and manufacture of nanoformulated medicines. They can be used for the rapid screening of formulation compositions and process conditions, and to develop the right drug delivery system. Essentially,

microfluidics pave the way for reproducible manufacturing to achieve uniform nanoparticle size distributions, which is very important for the efficacy and safety of a nanomedicine. Furthermore, the microfluidic process uses scalable because it is continuous.

Microsun exploits flow chemistry and uses the Nanoassemblr Blaze from Precision Nanosystems. The application of flow chemistry in a microfluidic set-up is advantageous for several reasons:

- When small-scale preparations (from milligram to tens of grams) are required – typically in small-volume, high-value business areas – waste products can be minimized and process analytics (in-flow detectors) can be integrated.
- It is typically operator-independent, with computer-controlled variables and easily cleanable/replaceable components.
- You can precisely control the geometry of fluid mixing, thereby allowing accurate control of solvent exchange and the ensuing self-assembly or precipitation phenomena.
- It is possible to run the process across microfluidic chips in parallel to produce the volumes of product required to support clinical development and commercialization – scale-out rather than scale-up.

Why Nanoformulate?

Traditional therapies are limited in the following ways:

i. Non-selective: they target healthy cells as well as diseased cells, resulting in toxicity whilst efficacy is poor becausethe quantity of drug at the target site is low.
ii. Short blood half-life: small molecules and peptides are rapidly metabolized or removed from the body, so large and frequent doses are required to achieve the right amount of drug at the target site (in some cases, this cannot be achieved at all).
iii. Multidrug resistance: targets can become resistant to the drug, where the drug is removed by/cannot enter target cells.
iv. Difficulty crossing biological membranes (for example, blood-brain barrier, gut wall, target cell membranes, and so on).
v. Poor physicochemical properties; for example, a lack of aqueous solubility or poor stability in the body.
vi. Small molecule/traditional biologic drugs are not suitable for many biological targets implicated in disease; new types of molecule are required (for example, nucleic acids), but they can be difficult to deliver to target sites and require cellular penetration and trafficking to the appropriate compartment in cells.

Nanoparticles, on the other hand, encapsulate active pharmaceutical ingredients (APIs) or biological nanostructures, with the following benefits:

i. Increased efficacy: more drug delivered to site of action.
ii. Decreased toxicity: less drug delivered elsewhere in the body, reducing side effects.
iii. Increased use of chemical space, providing access to a wider range of therapeutic modalities; for example, we can develop drugs that would otherwise be difficult or impossible to move forward.
iv. Enables evaluation of innovative and emerging therapies with potential to treat underserved diseases; for example, nucleic acids therapies, therapeutic vaccines, gene editing technologies.

How is Microsun being used?

We're using the platform in a number of 'real-life' systems. The industry needs more tools for preparing nanoparticles in a more space, time and cost-effective manner. When it comes to

Meet CPI

CPI works with business to translate inventions into products and processes that enhance health and well-being, protect and improve our environment and increase productivity across industries. Part of of the UK Government's High Value Manufacturing Catapult, CPI offers an understanding of innovation processes and financing, combined with industry relevant technical expertise and assets. The centre operates across many markets, including pharmaceuticals, speciality chemicals, food and drink, electronics, and transportation; and aims to help products and processes be quickly and cost-effectively brought to market, supporting the development of next-generation manufacturing. In 2014, CPI was awarded a £28 million grant to establish The National Formulation Centre, which works across a range of key technology areas and market sectors. Part of the grant is being used to develop capabilities for the UK formulation industry that do not currently exist.

increasing capacity and bringing more nanomedicines to market, we need more efficient approaches.

The Microsun project isn't just about microfluidics. We are also incorporating other advanced systems that can help with nanomedicine development, including technologies for the purification, real-time analysis and testing of finished products, which will be used to develop manufacturing processes for a range of complex nanomedicine technologies. In particular, the ability to monitor the quality of products in real-time, and to adjust the process to deliver in-specification materials, will be critical to the future success of our platform – these are essential attributes for the pharma industry.

What are the next steps?

The project will run for two years and we'll be aiming to:

- Demonstrate that a range of nanoformulations containing relevant active pharmaceutical ingredients can be developed rapidly using microfluidics.
- Evaluate the benefits of at-line particle size analysis and in-line formulation purification on control of product quality attributes and speed of process development.
- Demonstrate process optimization and scale-up of nanoformulations using parallel processing.
- Demonstrate the successful transfer of scale-up processes into GMP manufacturing facilities.

Collaboration is essential for this project – we need a variety of expertise. It's important to keep in mind that we all operate at different stages of the innovation cycle. If we talk in general terms around TRL (technology readiness levels), then academia is generally active at the TRL levels 1-3, with industry active across the spectrum. In this regard, multi-national pharmaceutical companies have a much greater focus than ever before on the internalization of novel concepts from the wider science community – and this typically requires external support to help translate early concepts into commercial reality.

The role of organizations like CPI is to help bridge the "valley of death" where many good inventions (by which we mean technically feasible and sought after) are not successfully commercialized. In the Microsun example, CPI is working to de-risk the innovation by providing open access facilities that remove the need for individual companies to invest in their own research infrastructure. Centers like this are also in a good position to collaborate effectively with academia to move new technologies through the TRL levels to make them more interesting and appealing to industry.

Reference

1. *Grand View Research, "Nanomedicine Market Size Worth $350.8 Billion By 2025 | CAGR: 11.2%" (2017). Available at https://bit.ly/2M0Bwqv. Last accessed August 3, 2018.*

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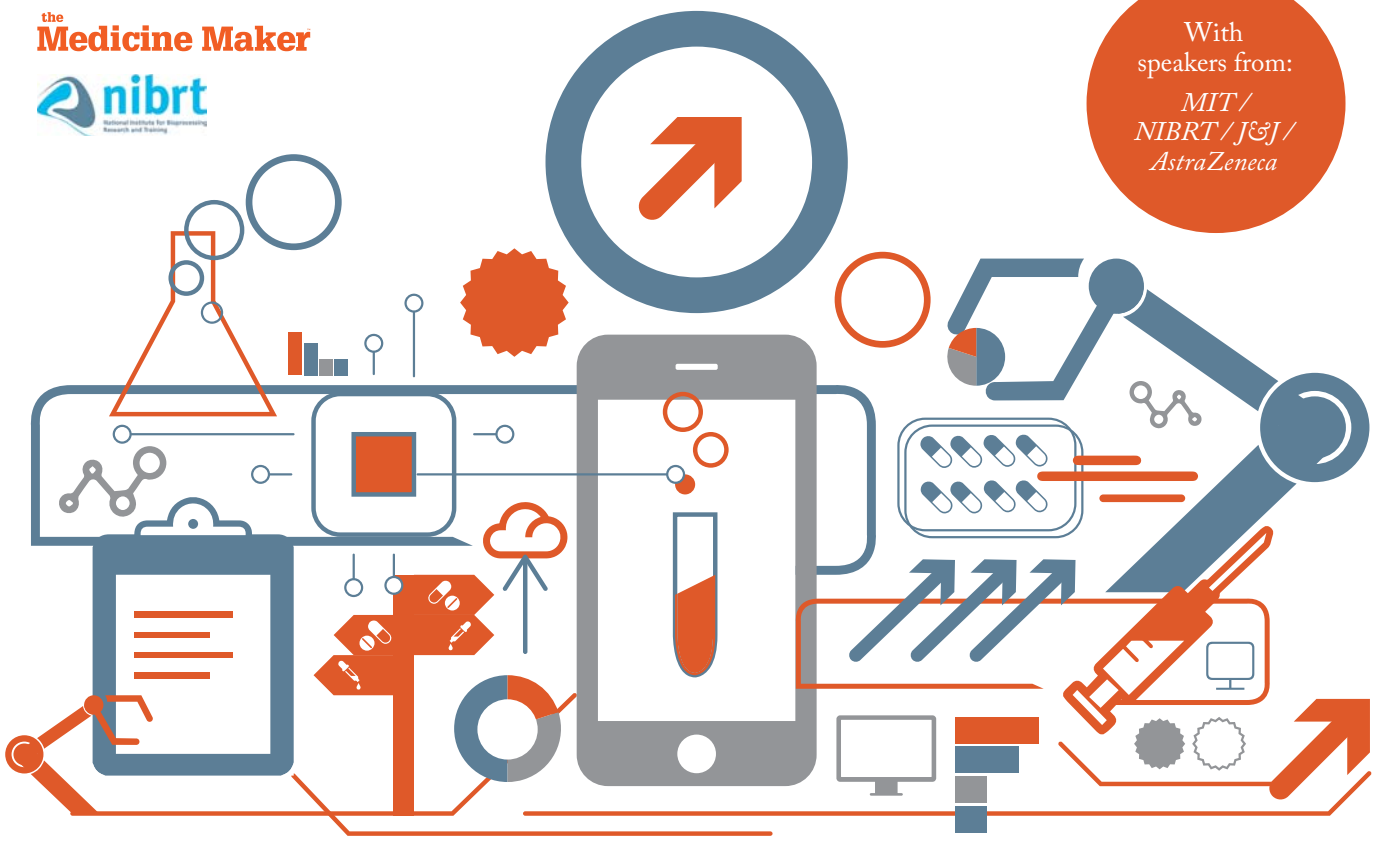

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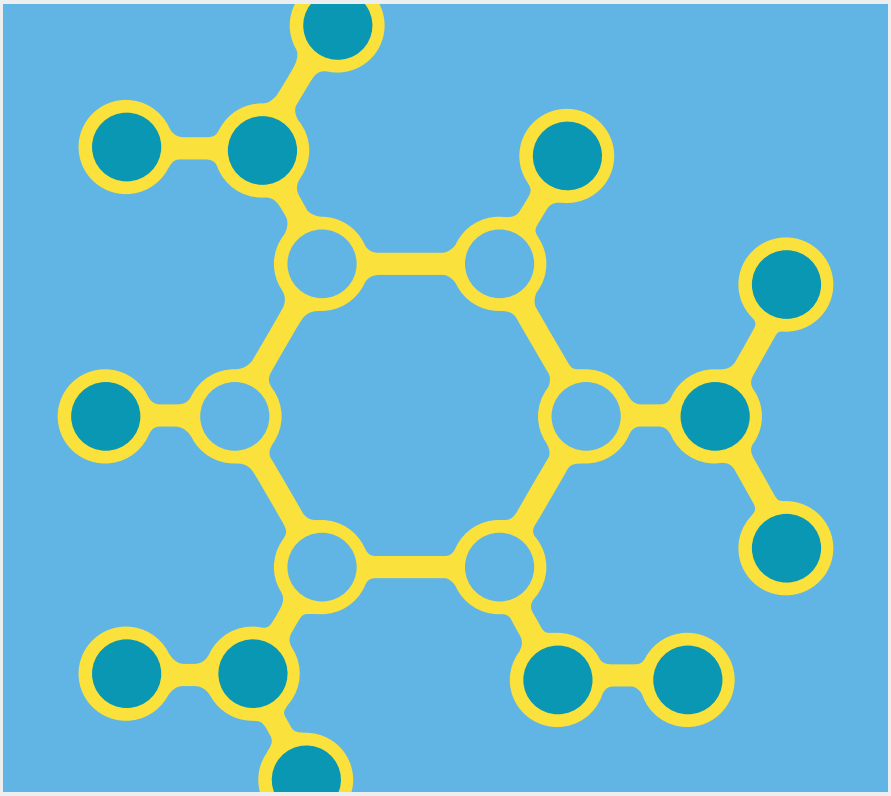
Cutting-Edge LC-MS: Essential Technology in the Pharma Toolbox

Where would drug development be without liquid chromatography-mass spectrometry – the hyphenated technique more commonly known as LC-MS? Here, we speak with expert LC-MS user Brunhilde Guessregen, who describes its importance in impurity profiling and structure elucidation at Merck.



What is your specific role at Merck?

I joined Merck in September as team leader for liquid chromatography-mass spectrometry (LC-MS) analysis for small molecules. Based on requests from Merck chemists, we perform LC-MS analysis on APIs – specifically, structure elucidation and impurity profiling – to support pharmaceutical development within the company. But we also get involved in other specialty analyses; for example, quantifying extractables and leachables in packaging.

As is typical in the analytical world, it is challenging work; many of the structures we need to elucidate are very complex, so it can be difficult to understand what is really happening in terms of degradation and side products. Good structure elucidation requires very experienced analysts – and I personally relish the challenge of the task! And it's also a pleasure to be able to work with cutting-edge technology in our endeavours – one big advantage of working at Merck!

"It's also a pleasure to be able to work with cutting-edge technology in our endeavours – one big advantage of working at Merck!"

Could you tell us a little more about impurity profiling – and why it's so important?

Impurity profiling is crucial to ensuring the quality and safety of the final drug product. During development, the API is well studied – and you'll know the mechanism of action and medical effects, as well as side effects. However, when synthesizing the API, side products are inevitable – and though they are typically only found in very small quantities, they can be highly active, leading to adverse effects or genotoxicity. Regulators, therefore, require in-depth reporting; you need to show what kind of impurities exist alongside your main component. Regulators mandate full characterization of your drug product, and have set specific limits for impurities; if we find an impurity within a certain range of concentrations, we need to elucidate the structure and also perform tests to assess genotoxicity. Not only is impurity profiling challenging, but it is also "high-stakes" analysis – we have to be fully confident in the results we produce, which means recruiting talented analysts and investing in the most sophisticated technology.

MERCK

"We analytical chemists are driven by the desire to produce highly accurate, top quality data."

What technology do you rely on in your laboratory?

In terms of LC-MS (shorthand for quite a diverse range of systems), we mainly use UHPLC or direct inlet via a syringe pump coupled with high resolution MS (time-of-flight mass spectrometry from Bruker or Orbitrap from Thermo Fisher Scientific) in our lab. LC-MS has advanced significantly in recent years and it's incredible that we now have almost benchtop-sized mass spectrometers with high resolution. Compared to the "older" sector field mass spectrometers they are also far more user friendly and easier to run! I just wish that the data from different mass spectrometers could be interpreted with one software tool, which could deal with data from all mass spectrometers.

However, it is important to remember that – as with many things – more than a single tool is needed for the job. As noted, to be absolutely certain about a given structure, impurities must be isolated and fully characterized. At Merck, we have different laboratories responsible for other specialist techniques that support our answers, such as nuclear magnetic resonance (NMR) spectroscopy and X-ray diffraction.

In short, we use whichever tool is most appropriate to the task – and, as a company, use as many tools as needed to be 100 percent confident (or as close as is humanly possible) in 100 percent of results! I don't believe that I am alone in considering "confidence" – both in the system and the results it produces – as the most important factor in analytical chemistry. We analytical chemists are driven by the desire to produce highly accurate, top quality data – and Merck chemists depend on us to do exactly that.

What is the most important aspect of your lab's role?

The biggest advantage of this is communication – I have the opportunity to speak directly to the chemist to learn more about the API. In fact, I love discussing analytical science and techniques with the Merck chemists we produce reports for. It's also great to be able to liaise with other labs within the company. When everything is under one roof, the system works as smoothly as possible. Contract lab work tends to be very commercially driven, and being in-house gives us the ability to really stay on top of problems. I really think that you can have much greater confidence in your results when you have generated them in-house and as part of a team. Every morning I start my day by talking with co-workers about our pending tasks, and throughout the day I'll be involved in meetings and telephone conferences about projects. I always encourage my staff to speak about their work and challenges with structure elucidation with other Merck scientists – that's how we can appreciate the challenges we each face, and grow as a team.

Faster for Pharma

Sitting Down With... Melissa Hanna-Brown, Analytical Technology & Innovation Lead, Pfizer Global R&D, Sandwich, UK.

What is your current role at Pfizer?
I coordinate Pfizer's pharmaceutical sciences external collaborations in analytical technology, which means bringing in new technologies that can accelerate the process of making new medicines.

You worked in academia previously…
I had a separation science lectureship in the pharmaceutical department at King's College, London. I love teaching – seeing the "lights go on." And I still teach separation science as part of my visiting position at Warwick University. My first role at Pfizer was technology-focused; I worked with the Pfizer Analytical Research Center, collaborating with people like Pat Sandra and Paul Haddad, so my role then was a hybrid between academia and industry. After that, I spent time leading analytical teams and learned more about the business, and now I've gone back to the technology side – but with a new understanding of how that technology is applied.

How did you find moving into industry?
It was exciting, but a big change. I went from having a lot of independence, to having to get "buy-in" from many stakeholders. It was a culture shock at first! I had to learn how to get people on board pretty quickly.

What appealed to you about the analytical side of pharma?
If I find something challenging, then I'll be interested in it. When I was 13, I got a weekend job in a pharmacy and I worked there until I went to university. One day, the pharmacist and I had a discussion on what bioavailability was, and he started drawing pharmacokinetic plots of plasma drug concentration with time and explaining to me what the area under the curve (AUC) meant. He told me some basics about how this was important in the drug development process, and I was intrigued by the measurement aspects and what technology was used to produce this information. I was inspired to look at careers in the pharmacy area, and did a pharmaceutical sciences joint honors degree with chemistry. The problem-solving element fascinated me, and still does – though what fires me up now is finding better and faster ways to solve problems.

What are the biggest challenges in the field?
At Pfizer, our technology strategy includes advanced manufacturing – moving away from the batch concept to a continuous process. The analytical challenge behind that is huge. We're used to doing in-process controls and taking samples away to the lab for testing; now, everything needs to be done online, with analytical sensors, miniaturization and microfluidics all posing particular opportunities.

Another area that affects the whole of pharma is predictive science. How can we be smarter about using knowledge we already have to save time? In chromatography, we're focusing on predicting retention times based on structure, to ensure good starting conditions for our methods.

How well does analytical science serve pharma?
It's always served pharma well, because it has to - analytical science is the glue that holds new drug applications together! We provide regulators with crucial proof about the processes we use to make medicine. Quality, safety and speed are always the drivers. We're being required to make medicines in a shorter amount of time – less than five years from proof-of-concept to development (rather than the 10 or 15 year timelines of the past) – but with the same amount of information. That's why modelling and computational science are increasingly important.

How else has the industry changed?
We've changed the way that we collaborate. Fifteen years ago, there were lots of one-on-one relationships, whereas now you see consortia forming around grand challenges in medicine development. For the pharma industry, that's significant; we now recognize that a great deal of the work we do to develop a medicine is pre-competitive; your IP is in your molecule, so work outside of that and if you can share with other companies and get regulators involved, it speeds up the whole development process. I think that's the way we will continue to work. We're all sharing data so we can build predictive models and do it even faster in the future. Collaboration is essential for innovation.

What are you most proud of?
I'm most proud of – and thankful for – the networks that I have built over the years. It's not the number of connections I've made, but the quality of relationships that I've nurtured that mean the most. Through my strong network, I have gathered mentors around me who I can always rely on for brutal honesty - but in a way that's always constructive.

Is the stigma of going into industry (rather than academia) real?
Students always ask: Will I still be able to do science? Will I be able to publish? You're always going to have to focus on projects, because that's what you are there to do – to get medicines to patients – but although the projects may look very different from what you could be doing as an academic, you are still applying analytical knowledge. I worked on an oncology drug for one of our first accelerated programs in Pfizer, and it was highly rewarding. In the pharma industry, the product of your daily work is actually having a positive impact on people's lives – it doesn't get much better than that.

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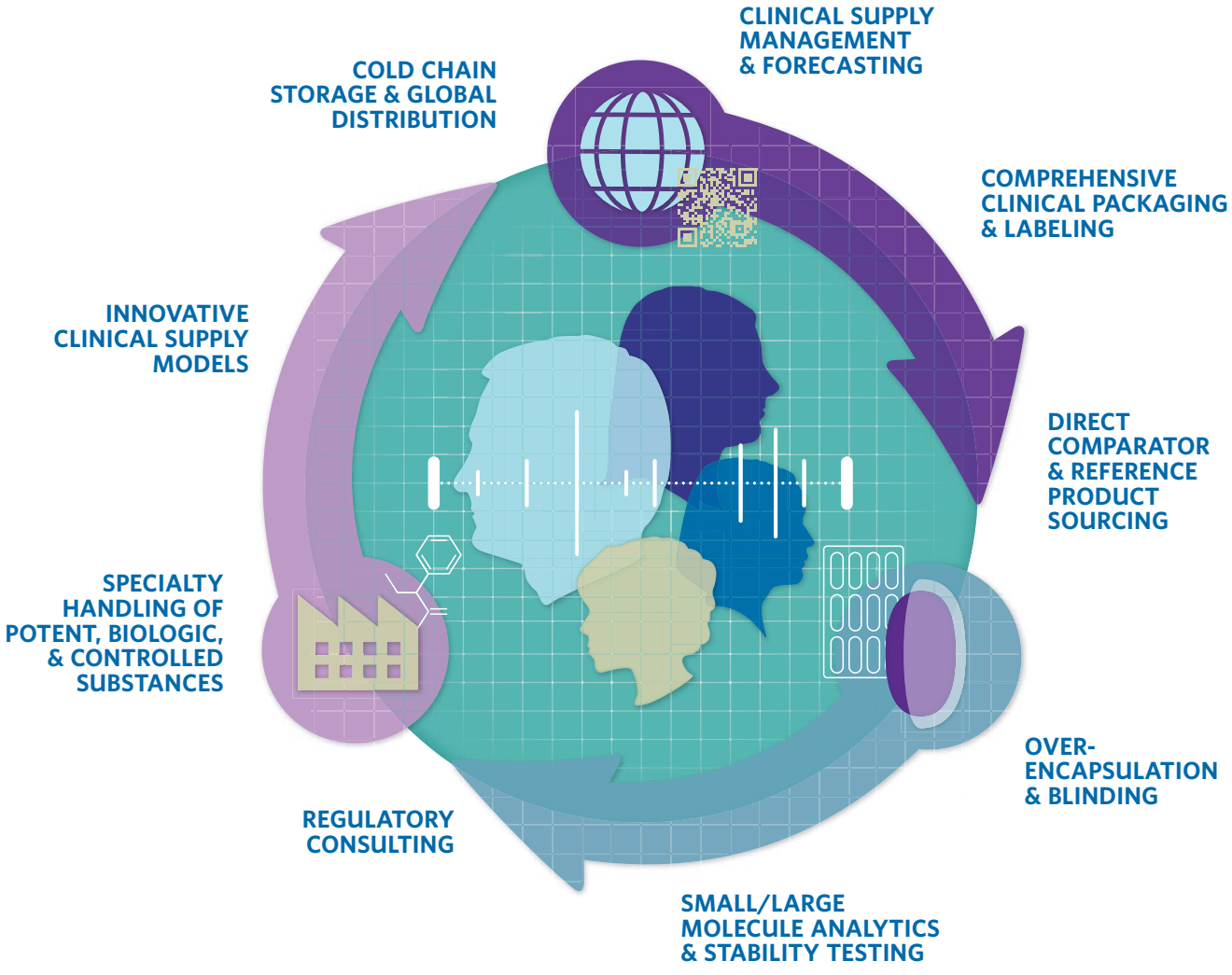

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