FEBRUARY 2019 # 50

the Medicine Maker™

50 ISSUES STRONG

Old and Forgotten

How can pharma better meet the diverse needs of the largest patient population?

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Online this Month

New Year, New Look

The Medicine Maker has a new website! The new site offers a reading experience that gives registered users content customization, where they'll only see the content that is of the greatest interest to their profession. Content can easily be accessed with a minimum number of clicks, making navigation and accessibility of content easier.

Globally, the publishing industry has seen that content consumption is increasingly a screen-based endeavor, with 90 percent of all media interactions through smartphones, laptops/PCs, tablets, and even television. So we're doing what we can to make the user experience as smooth as possible. The new website is more accessible and easier to navigate and read, without distracting or irritating banners and pop-ups.

Traditionally, our editorial team has worked to our monthly print deadlines – collating articles and publishing them in the magazine before uploading the articles to our website the following week. Now, following feedback from readers, who were looking for more interactive and current content, we'll be publishing online, as soon as the articles are ready. Of course our print magazine isn't going anywhere – we'll just be collating the best articles from the previous month's online content for print.

Our Content Director, Rich Whitworth, has described the new approach as "audience-first," in that we'll be closer to the issues that matter, celebrating successes all the sooner, and engaging with our communities more readily.

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the Medicine Maker

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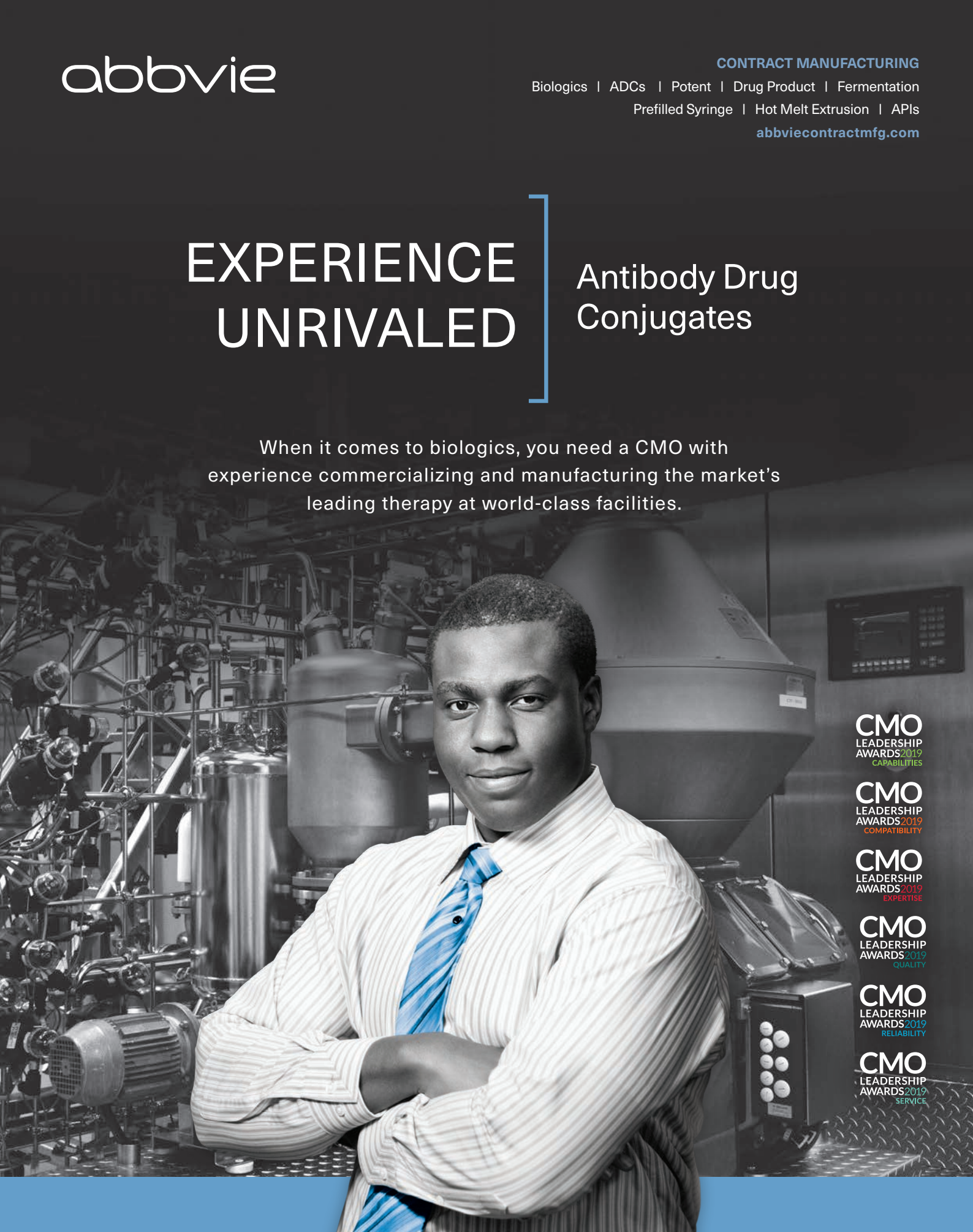
Antibody Drug Conjugates

When it comes to biologics, you need a CMO with experience commercializing and manufacturing the market's leading therapy at world-class facilities.



CMO LEADERSHIP AWARDS 2019 CAPABILITIES

CMO LEADERSHIP AWARDS 2019 COMPATIBILITY

CMO LEADERSHIP AWARDS 2019 EXPERTISE

CMO LEADERSHIP AWARDS 2019 QUALITY

CMO LEADERSHIP AWARDS 2019 RELIABILITY

CMO LEADERSHIP AWARDS 2019 SERVICE

In My View

Feature

Best Practice

Business

Sitting Down With

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Ask, and Ye Shall Receive

Regardless of how Britain leaves the European Union, the global pharma industry must always lobby for positive change.

Britain's departure from the European Union becomes a little less theoretical with each passing day. There was something poignant about the scenes in London last month, as EMA staff lowered the 28 EU flags in preparation for the Agency's move to Amsterdam. Whatever one thinks about Brexit on the whole, the loss of 900 highly skilled staff-members as well as the MHRA's leading role in European medicines regulation is hardly good for the UK. At best, it's collateral damage; at worst, it's like watching a "British success story" being broken up, as Mike Thompson, ABPI CEO, put it (1).

For me, the lowering of the flags symbolized Britain's separation from the EU's regulatory sphere – something the pharma industry was almost unanimously against (2). And something the UK government was hoping to avoid (in terms of pharmaceuticals), by asking to remain part of the EMA despite the contradiction with the its red line against single market membership.

The fact that the government would suggest such a thing implies that industry lobbying does have an impact. And though "no deal" is still on the table (I've been speaking to companies in the drug development space about their "no-deal" preparations – page 45), negotiations won't end on March 29 – there will be much still to play for.

The idea behind the formation of the EMA – hosted by London since 1995 – was to reduce the cost and time incurred by companies seeking separate approvals in each member state. By reversing this act of harmonization, companies will naturally seek approval in the larger EU market first, leading to delays for the UK. Will Brexit also reverse the process of global regulatory harmonization (a fear expressed by Ezequiel Zylberberg on page 48)? Or perhaps an independent UK could work with regulatory bodies around the world to increase harmonization amongst the larger markets... Either way, Britain will have to innovate to compete.

I believe this is what Mike Thompson meant when he said that Brexit would be a catalyst for positive change (3). He also told me: "politicians have great skill in going to the precipice and then turning back." As a very steep drop approaches, and the consequences for the industry begin to crystalize, let's hope he's right on both counts.

James Strachan
Deputy Editor

References

1. *The Guardian, "Britain loses medicines contracts as EU body anticipates Brexit" (2019). Available at: https://bit.ly/2LRtR9C. Accessed February 6, 2019.*
2. *J Strachan, "Hold Me Closer, UK Pharma", The Medicine Maker (2018). Available at: https://bit.ly/2GpCs4k.*
3. *J Strachan, "The Successful Experiment", The Medicine Maker (2018). Available at: https://bit.ly/2DbEv9d.*

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

THE INNOVATION AWARDS 2018

the Medicine Maker

Who's the Best?

Vote now for the top drug development technology of 2018

What?

Voting for the grand winner of The Medicine Maker 2018 Innovation Awards will end on Thursday February 28. You can vote now at http://tmm.txp.to/2019/innovationvote.

The Innovation Awards, published in our December issue (https://themedicinemaker.com/manufacture/innovation-awards-2018), showcased the most groundbreaking technologies released during 2018 that could have a profound effect on drug development and manufacturing.

Why?

When considering innovation in the pharma industry, new, groundbreaking medicines are the first to spring to mind – but the development of these medicines wouldn't be possible without innovation and dedication in drug development equipment and technology, from analytical systems, to filling equipment, to formulation technologies

How?

Nominations for the Innovation Awards were collected from readers during 2018. The entries were carefully evaluated and 16 top technologies were selected to showcase in the December issue.

Who?

The 16 top technologies of 2018 are:

- Co-creation of COC containers
- Colorista
- Cyto-Mine
- Endozyme II Go
- Eshmuno CP-FT
- LinearTwinScan
- Lyo-Check
- Master Data Collaboration Tool
- Microcell Vial Filler
- NovaTrack
- Orbitrap ID-X Tribrid Mass Spectrometer System
- Q Exactive UHMR Hybrid Quadrupole-Orbitrap Mass Spectrometer
- Smart Blister Pack
- syriQ BioPure
- UBERcellFLEX
- Zydis Ultra Coating Technology

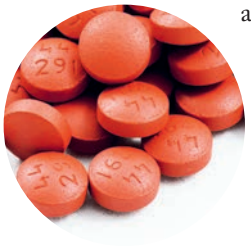
Which of these top technologies is the most innovative? It's up to you to decide! Vote now by filling out the online form at http://tmm.txp.to/2019/innovationvote.

We'll publish the development story behind the most popular technology in a future issue of The Medicine Maker.

Remembering Stewart Adams OBE

The inventor of ibuprofen died on January 30, aged 95

Back in the early 1960s, Stewart Adams – a pharmacist in the UK – had a bad hangover, but was due to speak at a European conference. The answer? Take the experimental drug that he had been developing with colleagues: 2-(4-isobutylphenyl) propionic acid – better known as ibuprofen. It worked a treat.

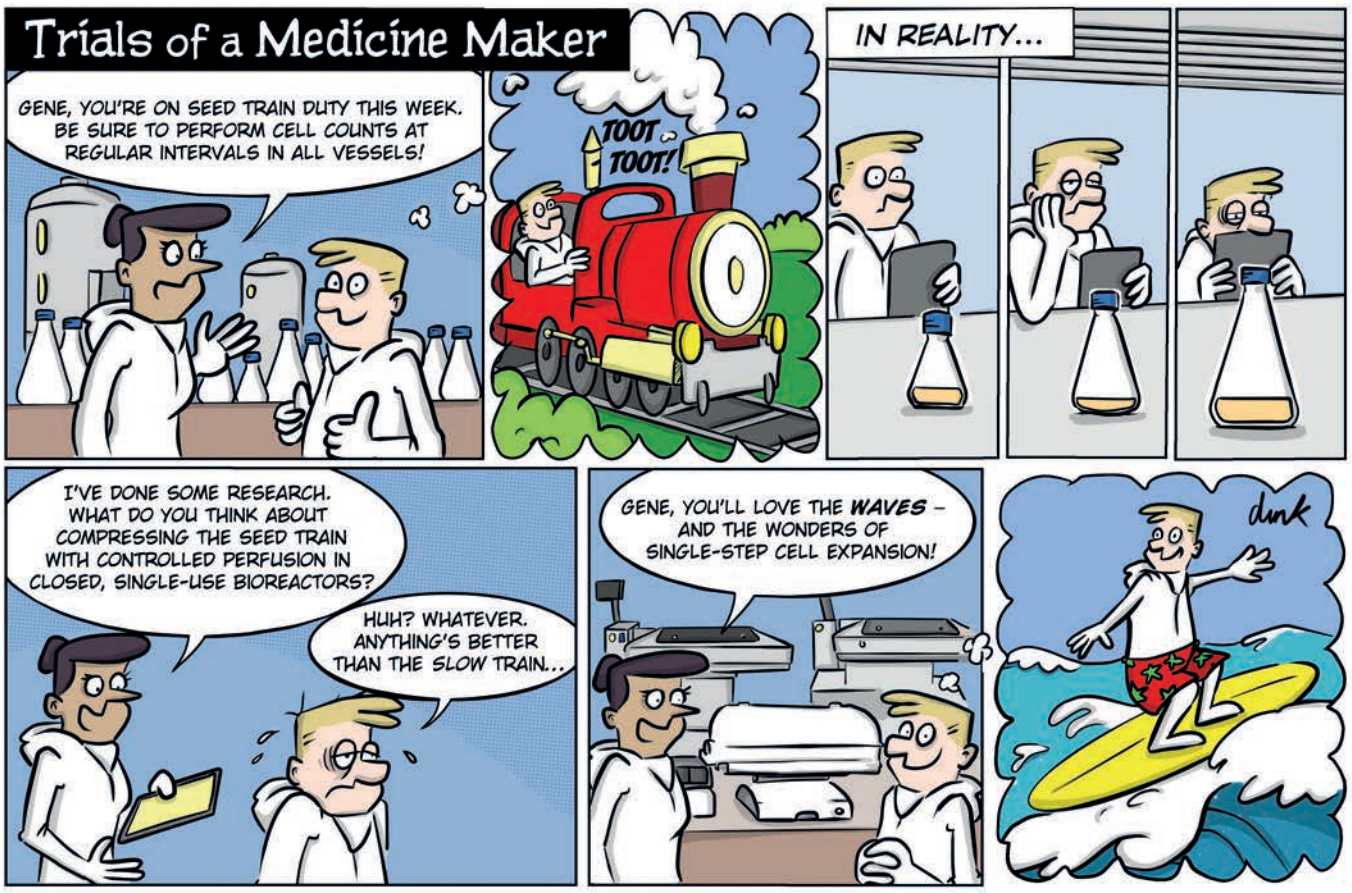


In 1969, the drug received its first approval as a prescription medicine (in the UK), but became available as an over-the-counter product in the mid-1980s. Today, ibuprofen is included on the WHO's list of essential medicines.

Adams was initially seeking a treatment for rheumatoid arthritis; while looking at other anti-inflammatories, he was struck by some of aspirin's disadvantages. The search for an alternative began, with Adams and his colleagues at Boots Pure Drug Company testing more than 600 chemical compounds in the process.

Adams was born in 1923 in Nottingham. He studied pharmacy at the University of Nottingham and started working at Boots Pure Drug Company in 1952. He died at the Queen's Medical Centre in Nottingham on January 30, 2019, at the age of 95.

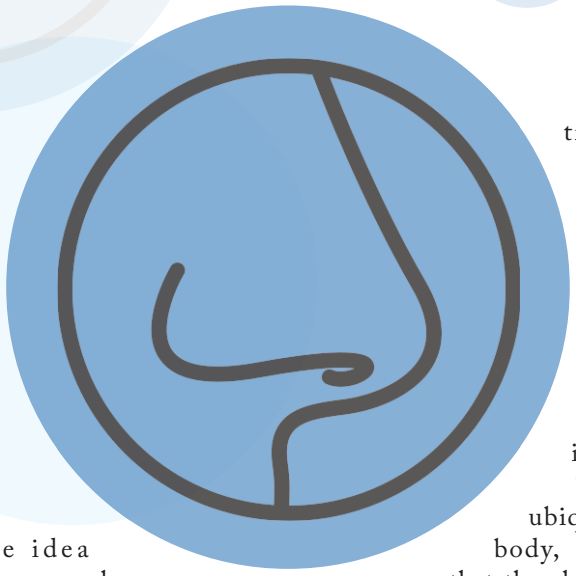
For more adventures featuring Gene and Eva check out our website themedicinemaker.com/additional-data/cartoons
If you have any ideas you'd like to see in future comic strips about bioprocessing then get in touch with us at info@themedicinemaker.com or look up #TrialsOfAMedicineMaker on Twitter.



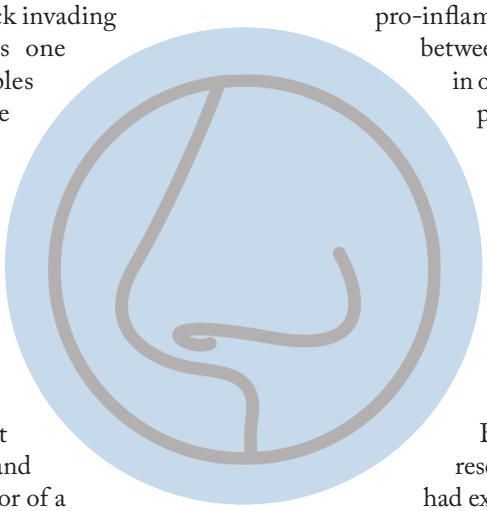
Brought to you by GE Healthcare

When Noses Counterattack

Mimicking the exomes secreted by nasal cells in response to bacteria could boost drug uptake



Each breath we take gives bacteria the opportunity to infiltrate our airways. Fortunately, our noses have their own effective mechanisms of defense. Researchers at Massachusetts Eye and Ear claim to have observed, for the first time, cells in the front of the nose detecting pathogenic bacteria in the nasal cavity. In response to bacteria, the cells release swarms of exosomes into the nasal mucus to attack invading microbes. "This is one of the only examples where the immune system actually extends outside the body (in this case into the airway) to fight off bacteria," says Benjamin Bleier, Associate Professor of Otolaryngology at Massachusetts Eye and Ear and senior author of a new study (1). "The detection of lipopolysaccharide molecular signatures in pathogenic bacteria triggers increased numbers of exosomes, packaged with antimicrobial molecules, to be released."



The exosomes employ a two-prong approach to defense: attacking bacteria directly with potency equivalent to antibiotics, and donating their antimicrobial proteins to epithelial cells by moving to the back of the nose through the natural mucus blanket where they are absorbed.

"The idea for this research came from our previous studies looking into the causes of chronic rhinosinusitis. We discovered that exosomes were secreted into the nasal mucus and were able to transport pro-inflammatory proteins between cells. However, in our healthy control patients, we also saw billions of exosomes being secreted, which led us to question what their role was in the normal healthy nose," explains Bleier. Though research at the time had explored the role of exosomes in gut cell cultures, no such information existed in regard to the nose.

Exosomes transport proteins between nasal epithelial cells on time scales that outpace mucociliary clearance (the movement of cilia on mucosal respiratory surfaces). According to Bleier, the efficiency of drug uptake via the nose could be improved if therapeutics were designed to mimic exosomes. However, as the composition of exosomes is similar to their host cells, they would likely trigger an immune response when introduced to a new host. Therefore, novel exosome-based therapeutics would need to allow rapid cellular uptake to occur, without eliciting an immune response.

"As exosomes are ubiquitous within the body, it is highly likely that they have a similar role in other organ systems too," adds Bleier. "Recent studies have also highlighted the cross-talk between the immune system and the human microbiome, so exosomes may also be responsible for maintaining a healthy commensal community in the nose by targeting pathogenic bacteria and tolerating healthy microbes."

Bleier and his team now plan to conduct large-scale bioinformatic studies to correlate the exosome proteome to the nasal microbiome, which could also have implications in understanding and treating chronic infectious and inflammatory disorders of the nose and sinuses.

Reference

1. *AL Nocera et al., "Exosome swarms eliminate airway pathogens and provide passive epithelial immunoprotection through nitric oxide", Journal of Allergy and Clinical Immunology, 18 (2018).*

Tiny Dancers

Could observation of waltzing therapeutic nanoparticles help determine drug efficacy?

By nature, the process of drug delivery is sensitive. The binding of a ligand at a cell receptor is akin to a dancer selecting a partner. A fine-tuned affinity is required for the partnership to work; binding that is too strong or weak can result in a failed interaction. The successful delivery of immunotherapies is a constant challenge, as is the ability to detect ligand-receptor interactions at a high resolution when trying to select the most effective immunotherapies.

Researchers at Indiana University have observed the rotation of drug delivery particles, providing detailed insights into binding at receptor sites (1). And, though the group has not delivered drugs into cells in this study, they hope their technique of detecting particle binding to receptors on cells will one day enable better screening of drug carriers with desirable properties.

"Conventionally, people have always thought that when particles bind to ligands, they will slow down and become 'trapped.' What they see is the translational motion of that particular particle," explains Yan Yu, an assistant professor at the Indiana University Bloomington College of Arts and Sciences.

Yu and her colleagues developed a technique that employs pairs of colored nanoparticles. In each particle pair, the dancing partner has a 200-nm green nanoparticle with a 40-nm red nanoparticle attached on the surface. By differentiating the particles with color, the waltz-like motion of the particle pairs (which begins with random rotation, transitions into a rocking motion, and then finally becomes confined to a circling motion) could be captured. "By measuring the rotation of these particles, we can garner more detail about how strongly these molecules bind to receptors. And this will allow us to screen molecules to discern which among them have the best binding to targeted receptor sites," explains Yu.

The researchers camouflaged the particles they used in their investigation. The particles were coated in cell membranes derived from T lymphocytes – which could make them good drug delivery vehicles. Yu's team also found that the particles were able to stay in circulation for longer periods than cells lacking the T-lymphocyte derived cell-membrane coating. Yu and her colleagues will now be using the imaging technique to investigate how their synthetic particles enter and bind to target cells during the drug delivery process.

Source: EFPIA, "The Pharmaceutical Industry in Figures. Key Data 2018," (2019). Available at https://bit.ly/2FTmKOL. Last accessed January 22, 2019.

Medicine Making in Europe

EFPIA figures give a snapshot of drug development and innovation in Europe

OVERVIEW

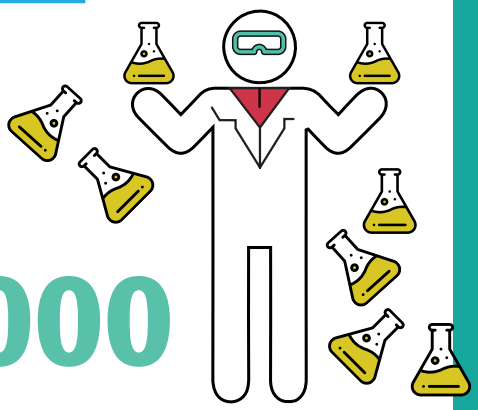
ONLY

2

OUT OF

10,000

substances synthesized in labs will reach the market



12 - 13 YEARS

will likely have passed before a synthesized substance reaches the market…

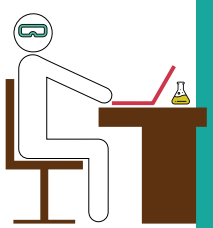
including

10 YEARS

of R&D

& 2-3 OF

of administration procedures

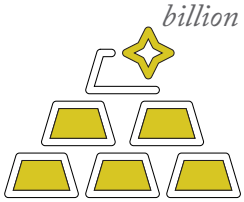


COST OF MAKING ONE NEW MEDICINE

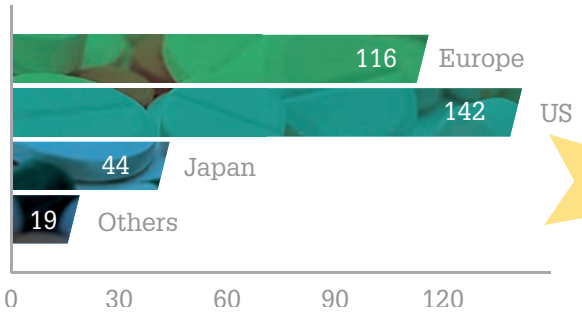
$2.558

billion

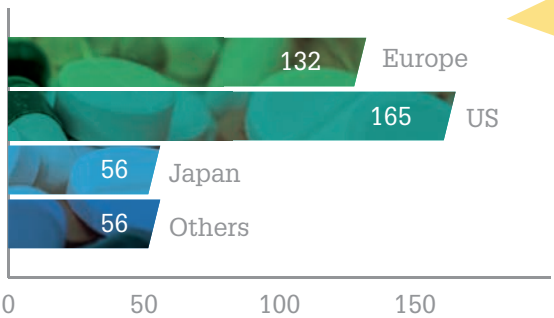
Number of new chemical or biological entities



1998 - 2007



2008 - 2017



THE RESULTS MATTER

Knee or hip replacements help prevent immobility

Targeted treatments exsist for some cancers

Today's European citizens can expect to live up to 30 years longer than they did a century ago

Cure rate for Hepatitis C

1999-2010: 41% with 48 weeks of treatment

2014-2015: 95-96% with 8-12 weeks of treatment

High blood pressure and cardiovascular disease can be controlled with antihypertensive and cholesterol-lowering medicines

Deaths due to HIV

2007: 2928

2016: 849

COUNTING COSTS

Total health expenditure in Europe in 2015

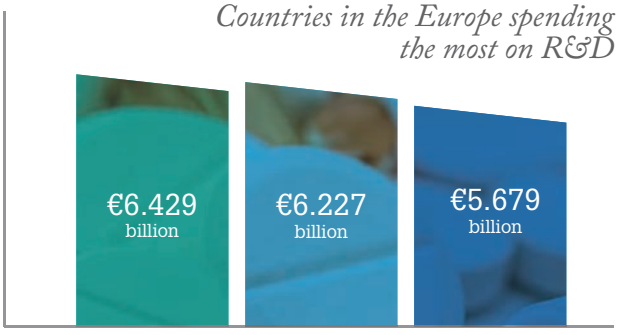
Outpatient care & others **39.2%**

In-patient care (hospital) **40.6%**

Medical goods (including drugs) **19.2%**

HEY BIG SPENDER!

Countries in the Europe spending the most on R&D



Solutions in... Drug Development

Douglas J. Swirsky, CEO of Rexahn Pharmaceuticals, explains his company's approach to developing more effective cancer treatments

The problem

There are no drugs currently approved to treat metastatic triple negative breast cancer. And for the majority of cancers with treatments available, there remains a significant number of patients for whom the drugs do not work – and we have a limited understanding of why this is the case.

Background

Although many standard chemotherapy drugs have been on the market for a long time, they may only work in around 60 or 70 percent of patients. For certain kinds of cancer, such as bladder cancer or malignant melanoma, the available drugs only work 20 to 30 percent of the time, and in some cancers it's as low as eight percent of patients. The reasons behind this are unclear, but it highlights why we need more personalized and precise treatments for patients. Immunotherapy drugs are one such approach, but when you take the brakes off the immune system, it can go into hyperdrive and begin killing healthy tissue in addition to cancer cells.

A solution

The founder of Rexahn was a cancer biologist, Chang H. Ahn, who saw the need to come up with drugs that exclusively killed off cancer cells. He started out by asking, are there any cancer-specific targets? Going back 10 years, in the early days of the company, work began by identifying specific drug targets. For example, UCK2, an enzyme overexpressed in tumor cells, and phosphorylated-p68, also selectively overexpressed in cancer cells. The latter modulates the activity of the β-catenin/Wnt pathway, which is involved in cancer cell growth and proliferation, oncogene expression and in the immune response to cancer.

Fast forward to today and we have two different drugs, RX-3117 and RX-5902, which are in midstage Phase II clinical trials, for different types of cancer. RX-3117, once activated by UCK2 and incorporated into the DNA or RNA of cancer cells, induces apoptotic cell death, and RX-5902, a small molecule inhibitor of phosphorylated-p68, decreases the proliferation or growth of cancer cells. We believe both drugs are cancer-cell specific and are well tolerated in patients – we are not seeing the kind of life-threatening toxicities that can come with other cancer drugs.

One of the collaborations we have is with a group at the University of Colorado. They showed that RX-5902 increases the number of T-cells entering the cancer cells and making the tumor more susceptible to being killed off by the patient's own immune system or by an immuno-oncology compound, such as Keytruda. We're actually collaborating with Merck (MSD) to see if this might work in practice.

Beyond the solution

Over the next few years, we hope to refine our understanding of the potential of our compounds as our clinical trials proceed. We recently announced that in our Phase IIa trial for metastatic pancreatic cancer with RX-3117 in combination with paclitaxel protein-bound particles for injectable suspension, one patient out of 24 had a complete response, eight had a partial response and 13 patients had stable disease, with an overall response rate of 38 percent. We are also looking forward to initiating our Phase II trial with the combination of RX-5902 and Merck's Keytruda in metastatic triple negative breast cancer. The future looks exciting!

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In My View

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

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

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

Phasing Out Inefficiency

Struggling with process research and development? Find yourself a CRO that knows what it's doing.

By Simon Tyler, Chief Operating Officer at CatSci Ltd, UK.

Drug developers are all too familiar with the numerous challenges faced at each phase of the clinical trial process. Solid chemical process research and development (PR&D) plays a crucial role in ensuring that the required amount of drug can be manufactured to the required quality in an economically and environmentally sustainable manner. Knowing just how important it is to get PR&D right across all phases, time and resource-squeezed organizations will often outsource projects to contract research organizations (CROs) – tapping into their additional expertise and facilities.

Though the relative importance of speed, quality and cost will vary across the drug development timeline for a new chemical entity (NCE), one important factor remains constant: risk management. When working with a CRO, potential challenges can be governed using effective communication. It is critical that both parties remain on the same page. The CRO should take the time to fully explore the broader contexts and objectives of a project, be able to grasp the chemical and technical challenges in detail, and be asking any questions that will allow it to create a customized solution.

Lines of communication should be kept open throughout the various stages and phases of a PR&D project; no doubt a customer's concerns will be dynamic and alter according to the uncertainties and risk associated with getting a molecule to market. Organizations looking to outsource PR&D need to know that their CROs are there to listen and support them through every challenge that may crop up across all drug development phases. Likewise, one must give CROs the opportunity to ask questions; they can't manage expectations effectively if they are kept in the dark about certain aspects of a project.

"Organizations looking to outsource PR&D need to know that their CROs are there to listen and support them through every challenge."

"During drug development, it is common to be constrained by both the clock and the budget, resulting in limited PR&D considerations."

During drug development, it is common to be constrained by both the clock and the budget, resulting in limited PR&D considerations. Balancing these pressures with successful risk reduction is the key to success. If the right process research is undertaken at the right time, across multiple phases, there can be a significant return on investment. Technical support is continually available when a drug developer partners with a CRO across a project, and an outsourcing organization's trusted expertise and experience can be exploited to operate with overall greater efficiency.

Increasingly, many organizations that develop novel therapeutics are considering next generation routes for NCE manufacture. An improved manufacturing route can be developed post-product launch or in parallel to initial drug development. The preferred time point for starting the manufacture of a next generation route will depend on the resource and time constraints that the drug developer has. If a manufacturing route has scope for improvement, you can start seeking such development support as early as phase II clinical trials. That said, it is natural for drug developers, who are financially or otherwise constrained, to be unwilling to spend time refining a manufacturing route. The logic behind this is that if a route is already safe and will provide a sufficiently early return on investment, then a next generation route is initially unnecessary. Consequently, the early focus is often on ensuring that an NCE can get to market as quickly as possible, but after this has been confirmed there is then scope for exploring how to improve the sustainability and profit margins of a route. Nonetheless, delaying the manufacturing route optimization may increase the risks of project difficulties in terms of material supply to feed clinical and other studies.

Any CRO that a drug developer chooses to partner with for PR&D must know how to time the range of activities that will ultimately secure the manufacture of the drug to meet research and commercial demands. This includes the development of any next generation routes that are required. Being able to effectively develop PR&D solutions for each phase of an NCE project requires a multitude of skills and experience. After all, PR&D is a balancing act of three key demands: speed, quality and cost, but also requires proficiency in risk management and communication. Good manufacturing is always founded on exemplary reaction understanding and process development. However, cost-effective risk management ultimately underpins the creation of phase-dependent solutions. Given that you will be investing a significant sum of money, it is imperative to know that your CRO will support you on your journey.

Taste the Rainbow

The color of a capsule or tablet can have a big impact on compliance and branding, but remember: decisions must be made early to avoid development delays.

By Nicolas Madit, Business Development Manager, Lonza Pharma & Biotech, Capsule Delivery Solutions.

Color has emerged as a critical design component of a medicine. Why? Color can have a big impact on patient compliance and is a great tool for brand recognition. Research shows that patients associate colors with certain feelings. Orange, for example, is perceived as warm, lively and stimulating, making it the preferred color for many stimulants. Colors can also differentiate a brand, improving recognition. Take Nexium for example – many people in the US likely know it as "the purple pill" that treats heartburn, and that the darker purple dosage form corresponds to the larger dose.

Another important point is security. Patients with a high pill burden may not be able to distinguish between various medicines of the same color. In fact, a few years ago, a diuretic drug had to be withdrawn after it was suspected that some packs contained a sedative. In fact, a geriatric patient had mistakenly taken the wrong pill because she had two different tablets that were both white and similar in size. If one had been a different color, the outcome may have been avoided. In addition, some colors may be easier for a child to accept rather than a white capsule or tablet.

"Ensuring you make the right decision early is key, but deciding on the final color isn't easy for formulators who may not be aware of its importance."

Despite its importance, decisions about which color to use are often made far too late in the development process. Formulators often start the development with whatever color capsules are available in their laboratory. But deciding to change the color much later means completely redoing the development phase as regulatory authorities only accept stability data generated with the final color of the dosage form. Choosing the right combination of fill and capsule color is crucial to success in developing your product right from the start.

Allow me to share a story from one of our customers. This company was racing to be "first to file" with the FDA and they launched development and stability studies for a pilot batch using standard colored capsules from their stock. But due to accelerated storage conditions, the capsules became crosslinked and the stability failed, requiring another stability test with that colored capsule. The failure prevented the company from filing the application and the stability process phase had to be conducted again. The direct estimated cost to reformulate was more than $100,000 and the risk of losing exclusivity linked to missing the "first of file" opportunity was even greater. By using a capsule that provides flexibility in the final color choice, the costly outcome could have been avoided.

Ensuring you make the right decision early is key, but deciding on the final color isn't easy for formulators who may not be aware of its importance. One way of getting around this problem is to use a capsule that provides flexibility in the choice of the final color, regardless of decisions made during the development stage. How? You can opt for a capsule that allows formulators to evaluate the stability of the fill with a large number of broadly accepted dyes and pigments at the same time.

Even with greater flexibility, expert advice is still often needed to guide formulators through complex regulations, and to refine their color composition to make it compliant in different markets. For example, some markets have restrictions on iron uptake, like in the US or Japan; or on dyes; for example, R3 is banned in Russia. It's much more complicated than just choosing the red or the blue pill!

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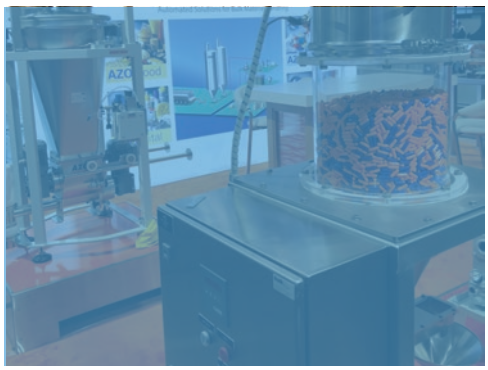

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More Than JUST A NUMBER

"Old age" is increasingly hard to define. The population to which the term typically refers encompasses a wide range of health issues and physical or mental capabilities. Comorbidities and polypharmacy go hand in hand, further complicating an already complex problem. More practically, swallowing a single tablet is impossible for some; for others, opening packaging represents a challenge – both drive noncompliance. What more can pharma do to help?

BY MARYAM MAHDI

Medicines often target a hypothetical patient population of homogenous adults. But the more senior demographic cannot be easily categorized. Commonly defined by the generic classification of "over 65," elderly patients differ significantly in terms of their physical capability and biological age, which can affect both how they interact with and respond to drugs. With global life expectancy on the rise, more and more of us have a good chance of reaching old age, but are there effective medicines waiting for us? Yes and no. An incredible number of therapeutic products are available, but are they tailored to the varied (but specific) needs of elderly patients, who may have trouble swallowing tablets or opening packaging? Some believe the elderly to be frail and always dependent on the care of others, but many elderly patients are perfectly capable of taking their medicines correctly – if they are designed to meet their needs. The exclusion of the elderly from clinical trials; complex polypharmacy needs; dysphagia; the increased risk of adverse drug events caused by lower organ efficiency… There is plenty of ground for the industry to explore when it comes to easing outcomes for geriatric patients.

(Too) slowly, the needs of an aging population are being recognized, triggering a shift in how drug development, formulation and even packaging is approached. In the following pages, we gather experts for their views on the plethora of issues faced by the elderly, and what pharma can do to better optimize medicines to this growing population's unique needs.

WITH AGE COMES… CHALLENGES, BUT NOT TRIALS

The elderly are the biggest users of pharmaceutical products but make up only a small percentage of participants in clinical trials. The reason behind this is obvious: elderly patients are complicated, and deciphering a drug's benefit-to-harm ratio in complicated patients is challenging. A key focus of Andrew McLachlan's career is understanding the impact of aging on drug disposition and response to medicines. Today, he is Head of the University of Sydney School of Pharmacy, Dean of Pharmacy, and Program Director of Australia's National Health and Medical Research Council's (NHMRC) Centre for Research Excellence in Medicines and Ageing. He's also a Member of the Order of Australia. We spoke with McLachlan to find out why the needs of the elderly are so often overlooked in drug development.

What are the difficulties in developing medicines suitable for elderly patients?

The elderly are very vulnerable when it comes to health conditions and often take multiple prescriptions for different indications. They are the biggest users of medicines and yet pharma development is not really adapted to their needs.

The current paradigm for drug development centers on healthy volunteers, and even when it comes to clinical trials in real patients, companies tend to recruit patients who are uncomplicated in terms of comorbidities. Elderly patients are likely to have a range of health issues – often of the cardiovascular system, musculoskeletal system, endocrinology issues and perhaps even mental health or neurological conditions – and are often excluded from clinical trials in favor of healthier, younger volunteers. How ironic that the very medicines brought to market as a result of these trials are not tested in the patients most likely to use them.

There can also be difficulties in designing dosage forms that are matched for elderly patients. Many elderly patients have swallowing difficulties, particularly with large tablets, but may also struggle to physically handle small tablets. Tablet design for the elderly is a whole other topic unto itself…

How does drug response vary between elderly patients and other patient groups?

Numerical age is not an indicator of biological age, and this can vary dramatically between patients. Most of us have probably met someone in their 80s who doesn't look a day over 70! But there are also people in their 60s who look like they are in their 80s. Some of this comes down to the way a person has lived their life, and some of it comes down to genetics. There will also be huge differences in how people of the same age respond to a medicine, which makes testing difficult. A group of patients all 80 years old may all require different dosages depending on the functionality of their organs. Research into aging biology is ongoing, but we do know that one of the major organs affected by aging is the liver, which is where we metabolize, process and eliminate many medicines. The immune system is also affected, and there are other aspects to consider too: old age often comes with nutrition issues and muscle loss. For these reasons and perhaps others, the elderly are more likely to experience adverse drug effects.

What does your research focus on?

Right now, there is a great deal we still don't know about the pharmacology of older people. In an aging society, we're all more likely to live longer than our parents or grandparents, and despite our improved health spans (periods of life marked by good health), the treatments available for the last months and years of our lives don't always contribute to quality of life. Growing old is inevitable and it is imperative that we fill the gaps in our existing knowledge about the elderly.

One of my particular interests is in polypharmacy and deprescribing. How can we safely de-escalate or reduce the number of medicines a patient is taking to improve their health? It's not about withdrawing treatment – although sometimes this is done upon request. When a patient is taking multiple medicines, we need to be aware that the balance between the benefits and harmful effects can change, particularly as patients age and become more susceptible to side effects.

For some older patients, there is no guarantee a medicine will work – and the WHO Global Patient Safety Challenge has flagged the need to prevent harmful effects of medicines as a priority. Polypharmacy has become the accepted solution to the management of multiple diseases but, in some cases, we lack a significant amount of information about drug-drug interactions. The burden of taking multiple medicines on a daily basis becomes particularly apparent in the elderly, who

RESEARCH EXCELLENCE

I've been working on the area of clinical pharmacology and older people for over a decade and led an Australian NHMRC Centre for Research Excellence in Medicines and Ageing for the last 5 years. Our research focuses on clinical pharmacology and pharmaco-epidemiology, investigating how medicines are used in older people and some of the patterns that can guide us on the optimal use of those medicines using real world data. There is a lot of data being gathered from clinical trials about older people but we wanted to take a new approach and generate our own, relevant to the Australian health system and implications for international health care. The center is also involved in training the workforce, which helps to raise awareness of the challenges of older people and medicines. I think it's really important to encourage people to challenge traditional paradigms of medicine and drug development. Consequently, we've published many research papers in this area, a number of which were published as part of a supplement to Advanced Drug Delivery reviews in 2018, available at https://bit.ly/2UHcblU.

may suffer from various conditions and struggle to manage (and remember) their medication regime. Some patients may be taking more than ten medicines a day. As the older adult patient demographic is typically more susceptible to adverse drug events than other groups, this can lead to healthcare practitioners prescribing drugs to treat the side-effects of other drugs, in what is known as the prescribing cascade. When patients begin to take more drugs than is useful or necessary, noncompliance rears its ugly head and thus the negative cycle of wasteful drug prescription continues.

In some cases, deprescribing begins with the aim of making a patient more comfortable towards the end of their life but, for some patients, health outcomes or quality of life may actually increase with deprescribing. There is a great deal of research in this area. Studies have also shown that the cessation of antipsychotic drugs in Alzheimer's patients has mortality benefits, for example.

What can pharma do to contribute?

There is a real lack of information from pharma companies about deprescribing and how to stop taking a medicine. The leaflet will contain a plethora of information covering clinical trials, dosing, how to start the medicines, how to increase the dose, and so on. But what about stopping a medicine? We never have complete information in this area. Can you just stop? Do you need to reduce the dose slowly? What about the possibility of adverse drug withdrawal reactions? What does the drug developer know? Because they will know something! We're actually working with the TGA in Australia to add in a section to product information about safely ceasing medication.

What other action is needed to better understand elderly patients?

Elderly patients are very vulnerable and are arguably the patient population where we need the most information about a medicine's safety and efficacy. Broader inclusion criteria in clinical trials that allow more elderly patients to take part would be of benefit. But from a financial perspective, bigger clinical trials result in larger costs. I strongly believe that pharmaceutical companies need to be remunerated for their investments because a viable and responsible pharmaceutical industry is essential for healthcare.

There is now an interesting array of tools at our disposal in the areas of modeling and simulation too, which could help improve understanding in terms of the pharmacokinetics of different dose concentrations and the responses in older people, ultimately helping pharma companies to better design drugs for the elderly. These types of technologies could also enable more personalization in the gerontology space. The current trend for personalization in the industry typically surrounds oncology in terms of targeting the right medicine to the right type of cancer, but we could make a huge impact on the elderly if we tailored therapies to them. And that might be as simple as providing a wider range of dosages.

Regulators also have a role to play. Drug development is influenced by regulators. Right now, it's not as if the pharma industry is doing anything wrong, but there are few regulatory mandates regarding the elderly (although the FDA has been ramping up efforts to include more older adults in clinical trials). Greater focus on the elderly from regulators could drive change in the industry; for example, a wider variety of medicines for children are now available because of regulatory initiatives and regulations in the pediatric area.

A MATTER OF FORMULATION

THE BIOLOGICAL PROCESS OF AGING CHANGES OUR INTERACTIONS WITH DRUGS. HOW CAN DRUG FORMULATION CONTRIBUTE TO PATIENT SATISFACTION AMONG ELDERLY PATIENTS? THE SIMPLE ANSWER LIES IN GIVING PATIENTS SOMETHING WE ALL ENJOY: MORE OPTIONS.

By Graeme Macleod

Essential as it is, the ability to swallow is often hindered by physiological changes to the neck, head and throat as we age. Senescence throughout the body results in poorer sensory-motor function and the possible development of dysphagia (difficulty swallowing). The condition affects one in 25 adults each year in the US and prolongs the first two anatomical phases of swallowing (oral and pharyngeal), resulting in choking and swelling discomfort when medicines are taken via the oral route of administration. The rapid growth of the senior demographic in the West means that dysphagia is becoming a more prevalent issue for health services, leaving pharma with no option but to assess the scale of the issue as it applies to economic strain and patient compliance.

In the production of novel drug products, development programs have to strike a balance between the specific needs of elderly patients and the economic benefit of producing such products. Though solid dosage forms like tablets and capsules are convenient and highly produced by the industry because of their stability, ease of transport and accurate dosage, they can often be too large for dysphagic patients. The last decade has seen the drug development industry take a step back and begin to consider the needs of different patient subgroups, most notably pediatrics; however, increasingly more focus is also being given to other specific patient groups, such as elderly patients. However, patient limitations also have be considered when developing alternative dosage forms. Chewable tablets, for example, may seem a logical replacement, but edentulism (toothlessness) and the use of dentures are prevalent conditions among the elderly – and an inability or difficulty to chew will ultimately result in non-adherence. Thankfully, regulators are increasingly asking companies to consider multiple patient centric factors including, chewing difficulty index (in chewable tablets) during the development of more convenient dose forms.

Orodispersible tablets (ODTs) have proven to bypass the issues associated with dysphagia and also avoid any chewing issues. According to FDA Guidelines, these tablets must disintegrate in the mouth in 30 seconds or less, in an effort to improve patient experience and overcome noncompliance. Their fast-disintegration may also be associated with increased bioavailability for certain APIs. However, it is particularly challenging to develop high dosages of APIs as ODTs. Tablets that have high doses of API can pose issues when it comes to achieving the desired balance between fast disintegration and tablet robustness. Development of such formulations can be made easier by using specially designed ODT excipient platforms, but ODTs can also require special packaging to ensure their stability and retained robustness, making their handling difficult for older patients who are more commonly affected by a loss of dexterity and motor function than younger patients.

Providing flexible formulation options to patients presents the opportunity to personalize treatment. This is particularly relevant in older patients where drug metabolism and biopharmaceutical issues can be more variable, meaning individualized dosing may be an increasing necessity. The dose of a liquid formulation, for example, can be adapted and tailored to suit both a 100 kg male patient with renal issues and a healthy 65 kg female elderly patient. However, liquids also have significant disadvantages such as poor stability and the inconvenience of carrying around a bottle. They may also be difficult for elderly patients to administer (due to increased incidence of tremor and co-ordination issues). Oral forms such as powders, ODTs and mini tablets can afford enhanced stability, give flexibility and are convenient to transport. Some products can also be packaged in sachets, making them easy to transport, as well as enabling adjustment of dosing.

> "MAKING THE RIGHT PRODUCTS FOR THE RIGHT PEOPLE IS (OR SHOULD BE) THE PHARMA INDUSTRY'S ETHOS"

The key for any given product development is to remember the requirements of the end user and to ensure it offers as much flexibility and convenience for the patient as possible.

That tastes... awful!

The palatability of a medication makes all the difference in how a patient interacts with it. Unfortunately, a large number of APIs are bitter-tasting, and though the older adult patient is comparatively less sensitive to taste than pediatric patients, they often take multiple medications daily, encountering their bitter tastes at a higher frequency than other patient groups. Despite

their more developed palates, dysgeusia, a distortion of taste, also affects older adults more than any other age demographic. Therefore, the suppression of off-putting tastes may do much to help increase compliance among the older population.

Taste-masking is an area that formulators must address during product development, but the development of new, taste-masked formulations can pose challenges. Fortunately there are an increasing number of technologies and approaches that the formulator can use, and again the decision on which approach to employ should reflect the specific needs of the API and the patient group...

Another challenge with taste masking is the toxic nature of APIs, which means we need alternative methods to test taste masking effectiveness. Methods such as electronic tongues, the rat "lick test" and use of cellular predictive methods are all being developed and improved.

The regulators' role

In the last couple of years, regulators have begun to actively address the needs of older adults. Last year, the FDA outlined its plan to include more older adults in clinical trials. Recent changes to guidelines also mean that data must be provided about the palatability and swallowability of a particular drug product. With the changing demands of regulators, development teams need to be nimble to react and ensure dossiers meet both the needs of the regulators, while also ensuring that new products meet the needs of older adults.

Making the right products for the right patients is (or should be) the pharma industry's ethos – it has a duty of care to the patients it serves. The emphasis should be on increasing quality of life for all patients. Over the last decade, we've certainly seen a significant shift in focus to the specific requirements of the pediatric population and the pharmaceutical issues pertaining to them. We need the same focus on the needs of the elderly, which are an increasingly large patient group with significant needs. Formulators can significantly improve quality of life via appropriate dose form design, but the industry and regulators need to build on recent impetus to enable this to happen...

Graeme Macleod is Global R&D Manager at SPI Pharma.

DESIGNING FOR PATIENTS

A LARGE, WHITE, UNCOATED TABLET IS NOT IDEAL FOR ELDERLY PATIENTS, IF COMPLIANCE IS THE NAME OF THE GAME. THAT'S JUST COMMON SENSE.

By Kevin Hughes

For too long, the needs of older adults were considered with an overly generic approach. Many in the industry would extrapolate data pertaining to children (in terms of swallowability, taste, and so on) and apply it to the elderly. And though there is some overlap in the challenges faced by both patient groups, they are clearly not the same. Older adults are the main market for many pharmaceutical products, so injections, tablets and capsules should be aimed primarily at that population. However, there is most definitely a lack of understanding when it comes to the needs of older people. Legislation has forced drug manufacturers to change their attitudes toward the pediatric population (there used to be a huge lack of appropriate medicines for children) but the same consideration needs to happen for the older population.

The EMA has taken steps to try to ensure that the quality of medicines is suitable for the older adult population.In 2013, the regulatory body published a concept paper which was followed by a reflection paper in 2017, entitled, "Reflection paper on the pharmaceutical development of medicines for use in the older population." The aim? To shine a light on the unique considerations that arise when developing medicines for older adults. The reflection paper was open for comments until the end of January 2018. Some within the industry felt that the paper should be more than a simple analysis of the situation; rather, they were seeking guidelines that forced the hand of formulators focus more intently on patient-centric design. The final guideline has yet to be published.

The FDA has also made a similar effort, publishing guidelines pertaining to the minimization of medication errors and product design, as well as releasing a guide to industry in 2015 that specifies the physical requirements that formulators should adhere to when developing solid dosage forms. In the US, I'm also seeing increasing focus from the FDA on patient compliance and human factors testing with medication, which is definitely a step in the right direction. In fact, it's becoming more commonplace for manufacturers to be challenged on these aspects of design. Given the increased scrutiny, I think key players in pharma will be compelled to do more to fill the information gaps that are so prevalent when it comes to developing medicines for older adults.

Indeed, some pharma companies now developing human factors departments where trials are now preference studies are conducted using patient groups representative of the older patient demographic. Swallowability, handling and the clarity of instructions are all considerations that these newly formed divisions work toward improving.

New tricks

When designing the right dosage form for the elderly, physical attributes are an obvious area to consider. Many medications are uncomfortable for any adult to swallow – and that's down to design issues. Some tablets still aren't even coated, for example. Coating is one straightforward method of improving swallowability – a coating system is available that makes a tablet very slippery when it comes into contact with liquid so that it can be swallowed with only a small amount of liquid. There is also size to consider. Large dosage forms can prevent the patient from consuming the medicine with ease and within a reasonable period of time. But smaller tablets can be challenging too; for example, patients with arthritis may find the handling of these tablets difficult.

Color is another oversight that can cause issues for older patients, who are commonly taking multiple medicines. How do patients reasonably distinguish the difference between several white tablets used to manage multiple conditions? It's easy to forget which ones have already been taken, and which ones need to be taken before, during or after a meal. Bear in mind that elderly patients can also suffer from visual impairment so colors with subtle differentiation may go unnoticed. In this case, different shapes of tablet could also be used. Colored and/or shaped tablets can help patients better identify their medications and give them the confidence to take them independently – and there are so many options that manufacturers can choose from that there is almost no excuse for a white round tablet! Dosage design specialists also

offer brand enhancement services that assess the requirements of various patient populations and examine the suitability of a particular size, color or shape.

Tablet design is not just about the way a medicine looks; coating can also help with stability. Manufacturers have a wealth of robust data, informing them of the stability of their products when stored in their primary packing, but many elderly patients (and many other patients for that matter) don't always keep medicines in the primary packaging. Patients may employ tablet boxes or caddies, for example, to manage their weekly medication schedules. This can potentially affect the stability of the tablet, so formulators should consider the types of coating they use and not rely on the primary pack as the main regulator of tablet stability.

"HEALTHCARE IS, AND WILL CONTINUE TO BE, A MASSIVE COST BURDEN FOR GOVERNMENTS WORLDWIDE."

Shifting the burden

Like any other patient population, the elderly can be made to feel inept or incapable when they are unable to correctly interact with their medications. By improving design features, the industry can do much to improve the quality of the patient experience. And in some cases, design features could also save a life. I was horrified to learn that it wasn't an uncommon occurrence for an older person to suffer from gastrointestinal perforation due to swallowing a tablet within a blister. The issue is not helped by the fact many blister packs are perforated, allowing single plastic cavities to be separated from the main piece of packaging, or the fact that small tablets can often remain trapped under the foil of the packaging. Healthcare workers and carers may have roles to play here, but so does pharma; we can't expect all elderly patients to be supervised when they take their medicines. Simpler options with clear instructions need to be provided to ensure that older patients are able to interact with their medications correctly.

Healthcare is, and will continue to be, a massive cost burden for governments worldwide. Manufacturers, therefore, often aim to formulate medicines as cheaply as possible, to be cost effective and competitive. Developing medications that truly appreciate the requirements of older patients and ensure improved patient compliance can feel low on the priority list, given today's economic and time restraints – but it's not as difficult or as expensive as you might think. There are many different options available that can help pharma companies make a big difference to the elderly.

If pharma companies take steps to design more patient-centric medicines, perhaps adherence can be increased, which should reflect in patient outcomes and help break down a false economy.

Kevin Hughes is Regulatory Affairs and QA Manager at Colorcon.

PACKAGING FOR ALL

WHEN CONSIDERING ELDERLY PEOPLE, WE CAN'T STOP AT DRUG DEVELOPMENT – PACKAGING NEEDS SPECIAL CONSIDERATION TOO.

By Stephen Wilkins

For elderly people, the gradual and persistent loss of dexterity, vision and hearing can contribute to the ability to read, handle and open pharmaceutical packaging, which in turn can affect medical adherence. For example, an elderly patient may fail to correctly prime an inhaler because of their poor grip strength or inability to read or understand instructions. They may be unable to muster the strength to open a blister pack. Moreover, fear or embarrassment of not being able to perform such tasks may prevent patients asking for help – even from those they are close to, further driving noncompliance.

But let's forget age for a moment: counterintuitive design is a limiting factor for us all.

Designers and manufacturers may feel that they must make their packaging as unique as possible to set it apart from competitor products, but it is essential that it doesn't create false affordances. Manufacturers should never assume that a patient will know how to use a particular piece of packaging. Elderly patients with dementia may even struggle with well-known packaging options. A friend of mine always used to say that if you design for the old you include the young, but if you design for the young, you exclude the old. I strongly believe that designers need to fully understand the challenges of sensory impairment and dexterity loss, which prevent older patients from being able to open packaging correctly. I have come across older patients who rely on tools to open packaging that is supposed to be opened by hand. Fingertip friction reduces significantly as we age. If you try dabbing your fingers in flour and trying to pick something up, the difficulty of that short-lived experience will inform you of an everyday reality faced by many older adult patients.

Senior-friendly standards

There is a lot that pharma companies can do to help matters. For instance, there are myriad charities with expertise in catering to elderly people and their specific needs. The Royal National Institute of Blind People undoubtedly has a much greater appreciation for the struggles of the partially-sighted and blind than the average person working in pharma. By forming connections with these types of organizations, a deeper understanding can be formed about the specific needs of the consumer.

The opportunity to create new packaging offers up other advantages for pharma companies. As raw materials will invariably be used to create new packs, the opportunity to incorporate covert anti-counterfeiting devices or taggers also arises, increasing the protection provided to all patients who use a particular pharmaceutical product and shielding the older population who typically have lower rates of medical literacy or knowledge from the harms of fake drugs.

On both national and international levels, there are also groups dedicated to ensuring the quality of packaging – and they have a great deal of advice to offer pharma companies. The International Organization for Standardization (ISO), for example, is a global network made up of 164 member countries. The organization is a world leader in providing clear guidance for products, services and systems, but adherence to its specifications is completely voluntary. One of the aims of the organization, however, is to maintain the quality of packaging made available to the public.

> "PEDIATRIC AND GERIATRIC PATIENTS PRESENT DIFFERENT BUT EQUALLY DIFFICULT CHALLENGES FOR THE PHARMA INDUSTRY."

Pediatric and geriatric patients present different but equally difficult challenges for the pharma industry. To ensure the safety of children, packaging should not be easy to open, but it should simultaneously be accessible to older adult patients who are more likely to

struggle with packaging openability than younger patient groups. Currently, there is no regulation available for adult openability, but ISO's child-resistance standards are often used as a measure of packaging suitability for the older patient population. The guidelines that can be used to test the ease of accessibility for older adults are:

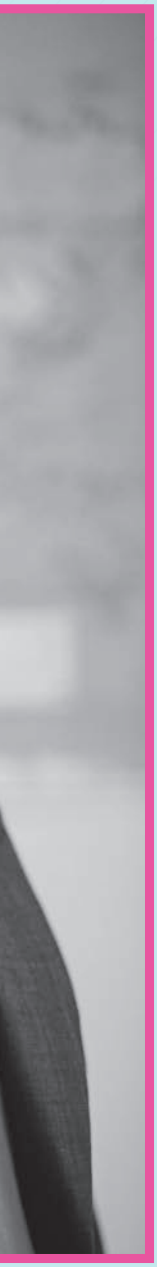
- ISO 17480: specifies accessible design for packaging with a focus on ease of opening
- ISO 8317: specifies performance requirements and test methods for reclosable packages designated as resistant to opening by children
- ISO 28862: performance requirements and methods of test for non-reclosable packaging that has been designated child-resistant and which is intended to contain non-pharmaceutical products
- ISO 13127: specifies test methods for mechanical testing of reclosable child-resistant packaging

Prior to any child-resistance test being conducted, all packaging must be tested to ensure that it closes correctly. Foil that fails to stick to a blister pack's train, for instance, would fail such testing.

For packaging to be considered child-resistant and senior-friendly, it has to pass tests in one of three ISO standards (ISO 8317, ISO 28862 or ISO 13127). The tests are made up of both a child and adult test. Eighty percent of children (aged between 42 and 51 months) should fail to open a pack within five minutes – including after being given an appropriate demonstration of how to do so. The adult test requires 90 percent of adults aged between 50 and 70 to open a pack and re-close it successfully within the same period of time.

Though these tests accurately determine the child-resistance of a pack, the broad inclusion criteria for adult volunteers means that the older patient demographic is poorly represented. ISO 17480, however, stipulates that only adults aged 65 to 80 years can participate in such testing, which enables packaging to be tested in patient groups that more accurately reflect this particular patient population. The needs of a patient with arthritis are not the same as a healthy patient. In short, taking into consideration the natural variability between older adults can only help improve the quality of future packaging.

Stephen Wilkins is the Director at Davies Development Testing Limited.



OWNER OF A LONELY HEART

By Jessica Finlay

In 2018, the UK's government appointed its first Minister for Loneliness. The role: to tackle loneliness (defined as an affective state reflecting the subjective experience of feeling alone or lonely) and social isolation (a measurable lack of social relationships) in Britain and though the role may be new to the British government, the problem isn't. Crossing generational divides, both loneliness and social isolation permeate throughout society, affecting people regardless of race, gender or social class. Importantly, loneliness and social isolation have been associated with a negative impact on health outcomes – and both are becoming increasingly prevalent among older adults. In the US, one-third of adults over the age of 60 are estimated to feel lonely and a quarter of over 65s live alone. Despite often being categorized as a social problem, the health implications caused by loneliness are significant. And as populations grow older, health related issues associated with loneliness and social isolation are becoming more pertinent for healthcare services. It is estimated that by 2050, there will be 2.1 billion people aged 60 or over worldwide, representing 21.3 percent of the global population (1).

Though the terms are often used interchangeably, loneliness and social isolation are two uniquely distinct concepts that are based on individual experience. It is not uncommon to be socially isolated and not have feelings of loneliness, and vice versa. Research has shown that many older adults who live in group settings (care homes) report loneliness.

Whether in conjunction with social isolation or not, self-perceived loneliness is detrimental to both physical and mental health. Many older adult who report feelings of loneliness also express feelings depression, lethargy and poor mental health. The sedentary lifestyle adopted by many lonely and/or isolated older adults is linked to poor physical health outcomes, including obesity, heart disease, diabetes, stroke, and even dementia and Alzheimer's disease.

The lack of sound research and evidence-based studies on the interventions that help to reduce loneliness among older adults is concerning. For those of us engaged in public health and gerontology, it is essential that we do more to fill the information gaps that hinder geriatric patient care.

There isn't a drug in the world that can cure loneliness. Its treatment requires multifaceted interventions that consider both the older adult and their context. The pharma industry can support older patients who struggle with polypharmacy – and tackle adverse drug events that may exacerbate isolation and loneliness among this at-risk population.

Aging, loneliness and disease are all interconnected. A more holistic approach to prescribing and managing medications can be developed to better match the needs of the patients most likely to take them – especially when they may be all alone. This has the potential to extend and save lives.

Jessica Finlay is an interdisciplinary doctoral fellow at the University of Minnesota.

References

1. *ONS, "Living longer: how our population is changing and why it matters". Available at https://bit.ly/2OxKFVc. Last Accessed January 15, 2019.*
2. *Age UK, "Loneliness". Available at https://bit.ly/2zWCHO4. Last accessed on January 15, 2019.*

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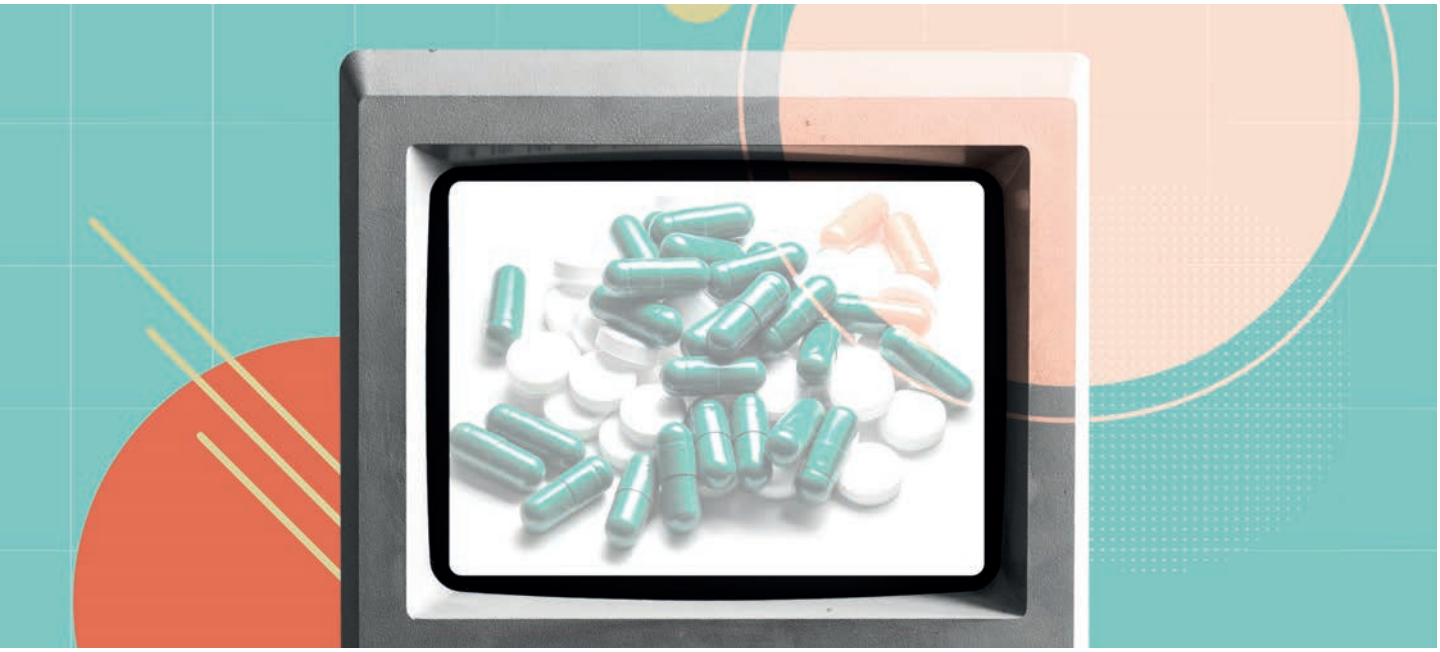

Taking a Byte out of Formulation Development

With so much technology at our disposal, it's time to get smart in formulation by adopting in silico approaches.

By Ronak Savla, Julien Meissonnier and Jan Neelissen

There are a number of technological advances that have helped drive improvements in small-molecule drug design – the sequencing of the human genome, increases in computing power, and high-throughput screening, to name just a few. Receptors and proteins that were once seen as undruggable at the cellular and sub-cellular levels have suddenly become more targetable. But drugs that are ligands for these newer targets are larger and more lipophilic (poorly soluble) than those in the past, introducing more biopharmaceutical and pharmacokinetic (PK) hurdles to optimal oral absorption and bioavailability.

Besides redesigning the chemical structure of the drug molecule, formulation development can help address these challenges. The primary goal of formulation development is to improve drug efficacy and safety by improving solubility and modifying the PK of the drug molecule, particularly absorption.

However, drug formulation is largely an empirical method that requires considerable time, material, and labor. Increasingly, companies want a fast "go/no-go" decision before spending more time and resources on a project. And ideally you want to get the decision right first time. Harnessing the power of in silico modeling and simulation technologies, along with more physiologically relevant, high-quality in vitro studies, should lead to faster formulation development, less attrition, reduced costs, and – most importantly – better treatments for patients. Modeling approaches can identify and predict oral absorption risks or liability factors, so that formulators can address the most pressing issues.

During the 2018 Controlled Release Society Annual Meeting in New York, we organized a panel discussion titled, "Inflection Point of Drug Formulation: Advanced In Silico Applications for Rational Drug Development." The focus of the session was how in silico technologies – solubility prediction and physiologically based pharmacokinetic (PBPK) modeling, and molecular dynamics simulations – influence formulation studies. In an ideal world, most (if not all) formulation development studies would be performed using computational tools with minimal reliance on in vitro and in vivo experiments. Unfortunately, despite advances in technology and computing power, most in silico approaches have yet to achieve the level of robustness to minimize or eliminate the empirical nature of formulation. Of these technologies, solubility prediction

"It is not always feasible in early product development to conduct in vivo studies."

is the most widespread, PBPK modeling the most advanced, and molecular dynamics the newest – representing the next generation of computational drug delivery tools.

Here, we focus on solubility prediction and PBPK modeling tools by providing a summary of the current state and insights on our experiences working with them. We look at these tools, in particular, because of their ubiquitous nature in drug development and importance in making drug formulation decisions.

A common problem

Solubility is one of the primary factors of oral absorption and exposure, according to the Biopharmaceutics Classification System (1), Developability Classification System (DCS) (2) and Biopharmaceutical Drug Disposition Classification System (BDDCS) (3). Solubility is perhaps the most commonly predicted molecule characteristic. Many pharmaceutical companies use solubility cutoffs, based on aqueous solubility, when selecting which compounds to advance for further development. But there are multiple formulation technologies including amorphous solid dispersions and lipid-based drug delivery systems that can improve solubility. We have three recommendations for integrating solubility predictions into drug formulation:

1. Solubility predictions should be taken with a grain of salt. Predictions provide guidance, but should be carefully understood before making formulation decisions. Compared with the original "General Solubility Equation," (4) whose inputs were melting and LogP, newer solubility prediction models, such as genetic algorithms and artificial neural networks, strive to establish quantitative structure property relationships (for example, molecular weight, polar surface area, aromaticity, rotating bonds), but are not significantly better at predicting solubility (5-7). It is quite common for different software to make different solubility predictions. One major reason for this variability lies in the complex nature of solubility. A drug's solubility is dependent on its molecular descriptors, composition of the solvent system, and molecular form parameters. These variables present a challenge to create uniform model training datasets for prediction.
2. Multiple solubility values should be predicted and/or measured in a variety of media and biorelevant buffers to more accurately and completely represent in vivo conditions. As an example, food effect is a major concern for poorly soluble drugs, such as protein kinase inhibitors. Comparing drug solubility in both fasting state and fed state simulated intestinal fluids can offer some insights as to whether the drug will experience significant food effect.
3. Solubility should be analyzed in relationship to the dose, as performed in the DCS. The DCS offers an equation to calculate the solubility-limited absorbable dose (SLAD) – the dose above which solubility is the limiting factor for absorption. Low solubility is not as big of a factor for drugs whose SLAD is greater than the dose compared with those drugs whose SLAD is less than the dose. For drugs whose SLAD is greater than the dose, solubility enhancing formulation technologies to improve absorption may make minimal improvement, whereas these technologies may be critical for drugs whose SLAD is less than the dose.

Pharmacokinetics at work

The gold standard of PK studies are in vivo animal and human studies, but these studies require considerable time and effort. Better understanding of physiology and introduction of in silico PBPK models, however, has drastically reduced PK-related attrition (8). PBPK modeling tools are based on mechanistic models that divide the gastrointestinal tract into compartments described by differential equations. The integration of these differential equations with drug characteristics (for example, pKa, LogP, particle size), formulation factors (for example, solubility and dissolution profile), available PK data, and gastrointestinal physiology (for example, gastric emptying, transit time) give the drug developer some level of predictive capability. And they can help companies choose the molecule with the best properties most likely to attain sufficient exposure, or choose a molecule whose PK challenges are addressable by formulation technologies. Some PBPK modeling tools also provide parameter sensitivity analysis (PSA), which can identify how certain formulation and drug properties affect PK properties.

The use of fundamental physicochemical properties of drug molecules and physiological values (for example, transit time, gut pH and volume) is called a bottom up approach. The fidelity of this approach relies on a selected set of measured or

predicted properties of drug molecules and physiological values of the gastrointestinal tract. A bottom up approach is often done early in drug development using off-the-shelf inputs, and prior to the completion of any in vivo studies. The goal is to gain insights into any challenges that the drug is likely to face, such as poor exposure and rapid or extensive clearance. As an example, lack of efficacy may be the result of poor target site exposure because the molecule has low bioavailability, the molecule does not distribute to the target site, and/or is rapidly cleared. In addition to PBPK modeling, the BDDCS uses solubility and permeability to model drug disposition, route of elimination, and effects of efflux and active transporters. According to the BDDCS, the majority of poorly soluble drugs are subject to hepatic clearance, so scientists should pay extra attention to understanding if solubility (the driving force for fraction absorbed) is the only hurdle to adequate exposure, or if clearance (gut wall metabolism and hepatic metabolism) are also potential issues. We've seen many instances (31 percent of poorly soluble molecule candidates, according to Catalent's latest analysis) wherein drug developers spend time and resources fixing one aspect, such as poor solubility, when the real issue turns out to be extensive first-pass metabolism or rapid clearance, for which oral formulation technologies are of minimal help. Therefore, PBPK models can help guide formulation development to address the correct issues.

Once some in vivo studies have been completed, PBPK models can also be built "top down" using PK values from animal studies to build more accurate human predictions. The data from in vivo studies in conjunction with PBPK models can also help with deciding on the optimal formulation pathway. PBPK models help set the target for formulation development studies and before beginning any formulation activity. We recommend that formulators understand whether complete or partial resolution of the solubility issue will result in achieving target PK parameters, as well as whether improvements in peak plasma concentration help if efficacy is driven by exposure. Such insights will enable formulation scientists to make the right trade-off between improvement in PK parameters, target dose, and drug load in formulation.

Finally, PBPK models help construct the oft-missing bridge between in vivo PK studies and in vitro dissolution models, and allow development of in vitro-in vivo correlation (IVIVC). IVIVC can then be used for quality assurance for different batches, or when formulation modifications are made to ensure the new drug formulation will have the same in vivo behavior.

Given some of the limitations of current in silico approaches, the best PBPK models should incorporate in silico, in vitro and in vivo data inputs, such as drug molecule physicochemical characteristics (molecular weight, logP, pKa, acid/base), solubility across the pH range, solubility in simulated fluids, and various PK characteristics, including permeability, plasma protein binding, and intrinsic clearance from in vitro microsomal and/or hepatocyte studies. A good model will allow for the determination of many PK parameters with a high degree of precision. Be aware, however, that the quality of the data inputs play a significant role in determining the precision of the predictions. Typically, in vitro and in vivo data are preferred over inputs from in silico predications, but it is not always feasible in early product development to conduct in vivo studies.

Time and effort!

Drug formulation is an important aspect of pharmaceutical development. And though this statement may seem obvious, many companies forego critical formulation activities and advance drugs with unresolved solubility and/or PK challenges resulting in drugs reaching the market with suboptimal and sometimes detrimental impact on the patients (9). In other cases, innovators focus their efforts and resources on a non-developable molecule because of inaccurate modeling and/or incomplete understanding of the real hurdles to exposure and activity. In either case, the time and cost of pharmaceutical development are driven higher with little-to-no patient benefit.

There are several formulation technologies that can help improve

solubility and absorption – and it's crucial that manufacturers understand these given the increasing number of poorly soluble drugs in the pipeline. Solubility prediction and PBPK modeling are useful tools to understand the potential challenges that each molecule may present, and can accelerate and guide candidate selection and formulation development. However, formulators must understand the caveats and nuances of these tools and not blindly follow outputs.

Good formulation development demands considerable time and effort – but the rewards justify the means.

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References

1. *GL Amidon et al., "A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability", Pharm Res. 314–420 (1995). PMID: 7617530.*
2. *JM Butler, JB Dressman, "The developability classification system: application of biopharmaceutics concepts to formulation development", J Pharm Sci, 99, 4940–4954, 2010. PMID: 20821390.*
3. *CY Wu, LZ Benet, "Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system", Pharm Res, 22, 11–23, 2005. PMID: 15771225.*
4. *Y Ran, SH Yalkowsky, "Prediction of Drug Solubility by the General Solubility Equation (GSE)", J Chem Inf Comput Sci, 41, 354–357 (2001). PMID: 11277722.*
5. *F Chevillard et al., "In Silico Prediction of Aqueous Solubility: A Multimodel Protocol Based on Chemical Similarity", Mol Pharm, 9, 3127–3135 (2012). PMID: 23072744.*
6. *T Sanghvi et al., "Playing Russian roulette with tyrosine kinase inhibitors", QSAR Comb Sci, 22, 258–262 (2003). PMID: 23340477.*
7. *J Huuskonen, "Estimation of Aqueous Solubility for a Diverse Set of Organic Compounds Based on Molecular Topology", Chem Inf Comput Sci, 40, 773–777 (2000). PMID: 10850781.*
8. *S Boyer, C Brearley, AM Davis, "Attrition in Drug Discovery and Development", Attrition in the Pharmaceutical Industry: Reasons, Implications, and Pathways Forward, 1st edition, John Wiley & Sons (2016).*
9. *RZ Szmulexitz and MJ Ratin, "Playing Russian roulette with tyrosine kinase inhibitors", Clin Pharmacol Ther, 93, 242–244 (2013). PMID: 23340477.*

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Mergers and Big Decisions

The CVS-Aetna merger could be a transformative event for the pharmaceutical industry. Shrewd negotiating decisions, analytics and real world evidence have never been more important.

By George Chressanthis and Randy Risser

US antitrust officials recently approved the proposed $69 billion CVS-Aetna merger, subject to provisions requiring Aetna to sell off its Medicare Part D business (1). The merger combines the third largest health insurance company (Aetna) and its 22 million medical members, with a pharmacy business (CVS) and its reach of five million retail pharmacy customers per day, 9800 retail outlets, 1100 MinuteClinics, and its powerful pharmacy benefit manager (PBM) business (1). This merger follows a similar action taken by the Justice Department to approve the Cigna-Express Scripts merger, and partnering activities by Amazon, Berkshire Hathaway, and J.P. Morgan to get into the healthcare industry. These events taken together suggest what some have characterized as "the era of retail medicine is fast approaching" (2). These changes also imply a looming battle between big pharma, large retail, big health insurance companies, and large pharmacies with their influential PBM programs. Clearly, change is coming to the historically insular pharma industry;

not from within, but from the outside – especially from business change-agents like Amazon and tech-giants.

Not everyone is happy about such developments. Some in the pharma and healthcare industries may see consolidation as threats. This quote from Barbara McAneny, President of the American Medical Association (AMA), is fascinating: "The AMA worked tirelessly to oppose this merger and presented a wealth of expert empirical evidence to convince regulators that the merger would harm patients." Why do physicians feel so threatened by this deal? Why do they feel patients will be harmed? It could be they see this merger as another big step in reducing their influence, caught between the mega-health systems and the mega-retail-insurance conglomerates. The creation of monopolies or a small set of stronger oligopolies means cutting costs and higher profits by limiting access to patient care. While "better outcomes," "higher value," "improved prevention," and so on, are all admirable goals that this and other similar mergers aspire to produce, in reality, CVS-Aetna will play hardball to exert their newly-created economic power in deals with pharma and healthcare systems. There is a delicate balance between managing costs versus maintaining or increasing quality of care and outcomes. Mergers like CVS-Aetna will likely shift the balance to the former at the expense of the latter. Both pharma and healthcare systems need to adapt to these changing dynamics.

There is no question that significant cost cutting is warranted. The healthcare sector has significant cost-structure imbalances (approximately 20 percent of US GDP is spent on healthcare) relative to outcomes generated, causing people to question the status quo. External change-agents are finding these conditions ripe for opportunities. CVS/Aetna can be seen less as change-agents and more as two healthcare industry insiders trying to adapt and position themselves in a changing landscape to protect their respective businesses.

Is the pharma industry prepared for such developments? Unlikely. These mergers and collaborative efforts bring together companies that better understand how to serve the customer, know how to leverage large amounts of data to improve outcomes, and have experience with transformative technologies such as artificial intelligence (AI) and machine learning (ML) to build better predictive models to diagnose and treat patients more effectively. Pharma companies would be well-advised to take notice and adopt the preceding areas of expertise to develop better customer insights and demonstration of value.

Mergers like the CVS-Aetna deal also place individual pharma companies at a disadvantage when it comes to negotiations over drug prices, formulary placement, and demonstration of value when entering into performance-based contracts (which will accelerate given these mergers). This is a big threat to pharma, as mergers like CVS-Aetna will likely focus more on negotiating lower prices and limiting access to branded drug therapies than on the "do-good" activities for patients, as touted by the CVS CEO: "Our focus will be at the local and community level […] to intervene with consumers to help predict and prevent potential health problems before they occur."

How should pharma companies respond?

The pharma sector is already undergoing rapid and evolving environmental changes, and the CVS-Aetna merger is an additional change that pharma companies need to evaluate. The important question is what should pharma companies do in response to this and similar events?

First, pharma companies must recognize that they can't be experts in all things, especially in those areas mastered by change-agent companies (2). Pharma companies have a "comparative advantage" of developing the basic science to produce novel drugs that address unmet medical needs – and they should stick to what they do best (2). But pharma companies need these capabilities mastered by change-agents to compete effectively, they need them now, and they cannot hope or wait to build these capabilities internally – the process will either take too long or will not be done right. Instead, we recommend that pharma companies partner with organizations that have deep and broad-base analytics, large database management, AI/ML, and pharma commercial operations expertise. This will allow them to leverage predicted outcomes from their drugs while also aligning with the objectives of patients, providers, payers (public and private), and pharmacies.

Second, pharma companies need to better understand and leverage the claims/electronic health record data space for commercial advantage. Roche's acquisition of Flatiron Health earlier this year for $2 billion was designed to get more involved with and increase access to real world evidence (RWE). RWE will be critical to show the benefit of personalized but expensive drug treatments, which are increasingly being seen in diseases such as cancer. The 21st Century Cures Act passed by Congress and avidly supported by FDA Commissioner Scott Gottlieb places a greater role for RWE in new drug applications for the demonstration of value-based evidence.

Third, pharma companies need to leverage AI/ML technologies for patient-centered predictive analytics. If healthcare is moving to a more retail-oriented and patient-centered industry, then applying AI/ML for real-time analytics will be crucial to ensure that contracted performance-based outcomes are on track to be achieved.

Aetna building, Hartford, Connecticut, USA.

Fourth, pharma companies need to partner with medical device companies to help with patient data collection and monitoring treatment progress. The use of medical apps is on the increase, and the data collected by smartphones and wearable devices will become increasingly important in quantifying "performance" in performance-based contracts.

Fifth, pharma companies need to find allies in the healthcare sector to counterbalance the growing influence from mergers. Consolidation is occurring in the healthcare sector between organizations like health insurance companies and pharmacies. We also see new competitors entering the fray that have no history or traditional mission within healthcare (e.g., Amazon, tech giants, large financial service companies, etc.). Therefore a key question is, who is a natural partner with pharma that can speak for patient care, access to the best medicines, and delivery of outcomes?

The quote from the AMA president suggests a fear of reduced access to quality healthcare, lower competition driving up prices, profits shifted to consolidated agents at the expense of other actors in healthcare, and healthcare decisions based more on cost containment than on delivery of outcome. Thus, a natural collaboration between pharma and healthcare systems (along with their providers) would be not only in their own mutual interests but also, and more importantly, to those of patients. These two groups are closely aligned, and together can ensure the identification of the best treatment options for patients and delivery of health and economic outcomes. This means pharma companies have to change their commercial focus and embrace what they are truly selling – not new prescriptions or boxes of product, but superior healthcare outcomes as a result of patients taking new medicines. This represents a formidable collaboration that can act to counterbalance the economic forces and concerns noted by the AMA president.

Collaborate to adapt

Is the CVS-Aetna merger a transformative event or more a response by inside-actors repositioning themselves in the shifting healthcare and pharma sectors? Strong arguments can be made for either case. However, it is clear that dramatic and structural changes are already occurring in the pharma industry. Significant economic forces will force change, whether pharma companies are ready or not. These significant changes are not favorable to pharma, which means pharma companies must manage both the disruption coming from outside the industry and restructuring happening within the industry as a result of these changes. These changes will increase the need for pharma to be very shrewd and calculated in pricing and contract negotiations. We believe the answer lies in the applications of analytics, the use of AI/ML to drive real-time insights and improve decision-making, better ways to commercialize RWE analysis, and demonstrating value. The good news for drug companies is that there are organizations already working within the pharmaceutical analytics area that can help them to navigate these challenges. Companies that adapt successfully to the changing times can use these environmental shifts as a source of significant competitive advantage relative to those that lag behind and fail to adjust. However, the time for pharma companies to act is now – delay is not an option.

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References

1. *The Washington Post, "CVS's $69 billion merger with Aetna is approved in deal that could transform health-care industry", (2018). Available at: https://wapo.st/2T6sTLc. Accessed January 21, 2019.*
2. *Forbes, "Aetna, CVS, Walgreens and Amazon may finally let pharma do what it does best" (2018). Available at: https://bit.ly/2U42rC8. Accessed January 21, 2019.*

Facing the Brexit Trial

A "no-deal" Brexit poses unique challenges for the drug development and advanced therapy sectors – not least tight timelines and a limited ability to stockpile. Here, we explore the potential pain points and find out what companies can do to prepare.

By James Strachan

Theresa May's Brexit deal was rejected in the UK House of Commons by 230 votes – the biggest defeat by a UK government in British parliamentary history. Following the record loss, the government backed an amendment tabled by senior Conservative backbencher Graham Brady, which seeks to replace the Irish backstop with "alternative arrangements." But within minutes of the Commons backing the plan, a spokesman for European council president, Donald Tusk, said the EU would not permit any changes to the deal already agreed.

The British position (no backstop, no single market, no customs union, no dependence on the ECJ), the Irish position (backstop, no hard border), and that of the EU (backstop, indivisibility of the four freedoms, no cherry-picking) are mutually exclusive (1). Unless a compromise can be found, the UK will leave the EU without a deal on March 29, 11pm London time.

Hard Brexit looks more likely than ever. And it's up to pharma companies and the government to put in place plans to minimize the impact on patients. We've written previously about the fragility of pharma's supply chains, with ingredients and products often crossing UK/EU borders multiple times in the development, manufacturing and distribution process – sometimes being "dropshipped" directly to customers within 24 hours of an order being placed (2). There's a real concern that regulatory uncertainty and delays at borders after a "no deal" Brexit will result in shortages of approved medicines.

The drug development industry also faces real problems if hard Brexit comes to pass. If companies can't deliver materials used in ongoing clinical trials, then there's a risk patients could miss doses. Of course, this could delay regulatory approvals, but for the individual patients enrolled in trials, it could have serious immediate consequences.

"There are patients in late stage oncology trials that are really relying on these investigational products," says Paul Hegwood, President of Clinical Supply Services at Catalent. "Missing a shipment and a patient dosing can be catastrophic. The clinical supplies industry, from sponsors to clinical

The UK Government's No-Deal Plans

The EU has been very clear from the beginning as to what Brexit will mean for UK-based pharma companies. The EMA's preparedness notices state that the UK will be treated as any other third country—with MAs, orphan designations, batch release, Qualified Person Responsible for Pharmacovigilance, and Pharmacovigilance System Master Files, all needing to be transferred to the European Economic Area before March 30. But how will the UK government approach regulation post-Brexit? And is there anything it can do to prevent medicines shortages in the event of no deal?

The UK government has said that it will continue to accept batch testing of human medicines carried out in countries named on a list set out by the MHRA (3). The government has said this would include EU countries, other EEA countries and those third countries with which the EU has an MRA. With regard to clinical trials, the UK will also continue to accept batch testing of Investigational Medicinal Products manufactured in the EU and EEA. The government has yet to publish its guidance on biological medicines, IT systems requirements, manufacturing and import licensing, but says the guidance is forthcoming.

In addition to asking pharma manufacturers to stockpile six week's worth of drugs, it has also said that medicines and medical products will be prioritized (ahead of food, for example) on "alternative" roll-on, roll-off freight routes after March 29 (4).

And in the event of a serious shortage of prescription medicines, Ministers will be able to issue a "serious shortage protocol" so that pharmacists can dispense different quantity/strength, or a different medicine altogether (5).

More broadly, the government recently announced that in the event of no deal, importers will be able to transport goods into the UK from the EU without having to make a full customs declaration at the border, and will be able to postpone paying any import duties, under HM Revenue & Customs' "transitional simplified procedures" plan (6).

supplies organizations, are dedicated to finding ways to make sure this does not happen as a result of a 'no-deal' Brexit."

Putting on a supply clinic

A major problem for companies is taking action in anticipation of an event, which at the time of writing is still only a possibility – one which all sides are determined to avoid. Hegwood says there have been a range of responses from drug development companies. "Some sponsors have taken a low risk course of action and they've decided to ask us to move supplies from the UK to our site in Germany, which allows us to continue distribution without issues," he says. "Other companies have asked us to do impact studies, and there are some who are still in the 'wait and see what happens' mode. Once we get a definite decision I think there may be a surge in activity as companies start moving to protect supplies or, if it's not hard Brexit, everyone will stand down."

Problems may arise if too many companies wait until the last minute to take action. Catalent has been working with companies to bulk up supplies. "This should help provide some additional runway. If we have released supplies in the UK before March 29, we can continue to ship those from a quality and regulatory perspective into the EU. So with additional supplies we can buy more time to react in the event of a sudden no deal."

Having to ship urgently isn't unusual in the clinical trials business, as companies marry up investigational products with a regionally recruited patient. Catalent has put additional resources into this area in case a company isn't fully prepared. "Importer of record services, VAT services, import licenses and approvals... these areas are going to need a lot of attention," says Hegwood. "So we have put in place a 'special service team' of logistics people to help us navigate across trade barriers."

Companies might also be faced with the physical challenge of moving products across borders, if ports and roads become slow or unmanageable after a sudden Brexit. But the administrative burden associated with no deal is arguably the bigger problem. As with approved products, clinical trial materials exported from the UK to the EU after Brexit will have to be certified once supplies have entered the EU by an EU-based Qualified Person (QP). "It's a very specific capability and QPs are personally accountable when they approve and release a batch. It's always a challenge to find experienced QPs," says Hegwood.

In our previous feature (1), a major concern for Sascha Sonnenberg, VP Commercial Operations Americas and EMEA at Marken – a company that specializes in supply chain solutions for clinical trials – was that a shortage in

QPs could "delay or endanger ongoing trials." Hegwood agrees that companies may be scrambling to find more QP capacity in the event of no deal, but that there are contract agencies that offer QP services and QPs that work on a consultancy basis. "I think there's enough capacity to go around."

Hegwood believes the biggest challenge will be faced by those UK-based companies that don't have any facilities or legal entities in the EU. He suggests such companies look at working with a partner that has locations on both sides of the border to get them though the Brexit transition.

Advanced therapies; advanced problems?

The advanced therapies sector is another area of particular concern. Materials in this sector are often living cells with very short shelf lives, and the patients being treated – either with approved products or treatments in clinical trials – are often very ill. Many of these therapies are autologous, which means cells are taken from a patient, shipped to a manufacturing facility to be manipulated, then shipped back to the patient for treatment. "You can't stockpile because products are manufactured on a patient-by-patient basis," says Matthew Lakelin, Chief Scientific Officer at TrakCel – which provides technologies for companies moving cell therapies across borders. "It presents some unique challenges."

Lakelin believes courier companies are key to getting it right. "We would strongly recommend using a premium courier company," he says. "They have operatives that understand import and export legislation associated with these products. They also have boots on the ground at customs so that they can get the products through."

Having a cultural understanding of these products is perhaps more important than in other sectors. "The best courier companies understand that they hold a person's chance of a life in their hands when they carry the products into their van," says Lakelin. "This can prevent many simple logistical errors. They also have the ability to store products at the correct temperature in validated units while waiting for customs clearance."

Can a white glove courier guarantee that there won't be any problems at this stage? Lakelin thinks it's difficult to guarantee anything. "Normally, if you're trying a new shipping route for example, you'd run some test shipments. But you don't have the luxury of this approach if you already have a clinical trial ongoing or a marketed therapy where patients need supply," he says. But there are some extreme steps companies are able to take due to the small volumes involved; for example, Lakelin says that companies can have products hand carried onto airplanes and delivered in person. This is commonly done for stem cell transplants – the Anthony Nolan group (a UK-based charity) have volunteers who will deliver a bag of stem cells at the drop of a hat to a patient. "Courier companies can provide this service, but they don't have any volunteers so it is incredibly expensive," says Lakelin. "It wouldn't really be feasible in the long run. And if there isn't an agreement in place to keep planes flying, there could be major problems for the industry and for patients."

Uncertain times

In our most recent Brexit article (1), David Jefferys, Senior Vice President for Global Regulatory, Healthcare Policy and Corporate Affairs for Eisai Europe, and Chairman of Eisai's Global Regulatory Council said, "When companies are thinking about investing in the UK, the uncertainty is definitely having a negative impact." And the clinical trials industry is no exception – especially in the face of a no-deal Brexit.

"We will do everything humanly possible to make sure that we can get clinical shipments through."

"For about a year now, our European customers have avoided the uncertainty around Brexit by not planning to open or actually opening clinical trial sites in the UK," says Lakelin. "The major challenge for UK-based companies is that they have to get their products into Europe and back again, and we know of at least one that has opened a secondary manufacturing facility in mainland Europe."

Miguel Forte, Chief Executive Officer of Zelluna Immunotherapy, says they have considered doing a clinical trial in the UK, but then uncertainty around Brexit flared up. "The UK has a lot of centers of excellence for cell and gene therapies, which we would appreciate being able to access. Plus, the MHRA is a very knowledgeable authority to go to for advice," he says. "But the uncertainty around the regulatory environment in the short to medium term is a negative impact factor in our decision."

Ezequiel Zylberberg, Strategic Alliances Manager at Akron Biotech – a US-based company that provides raw materials and manufacturing services/technologies for the production of advanced therapeutics medicinal products, says that sudden potential changes in the regulatory environment as a result of Brexit is creating uncertainty for his company and his clients. "It may shape our clients decisions in terms of where they choose to conduct their trials. However, decisions around clinical trials management take a long time to materialize, so the full impact on business likely won't be felt for a year or two," he says. "I'm not sure companies are ready to completely change strategic direction before we have an answer on the legal framework."

For Akron, Zylberberg is mostly concerned about the effect on global regulatory harmonization of GMP regulations. "What do we mean when we say an 'ancillary material was produced under current GMPs'? The industry has not coalesced around a single definition and I think geographic fragmentation will lead to a greater fragmentation in our language. And that's one of the things we're worried about," he says. "An event like Brexit really reasserts the importance of working with with international organizations, such as ISO, to make sure we have common nomenclature. Because if the cell and gene therapy industry is to reach its potential, we need to be speaking the same language."

Mitigation limitations

A major problem for companies is understanding how a no-deal Brexit may play out in practice. Many have anticipated long queues of trucks leading up to UK ports as a result of new checks on the EU side. But it is unclear whether controls on the EU side will be implemented in full on Brexit day. Plus, some haulage companies may refrain from exporting until they know exactly what will be involved – some companies may also conclude that the new costs associated with trading with the EU aren't worth it. These factors could combine to reduce port traffic and delays in the short term. Then there's the possibility of Article 50 being extended – or even revoked altogether. Is the most likely outcome of all that both sides can come to an agreement akin to the Withdrawal Agreement? Perhaps, but nobody at this stage dares rule out the worst predictions of no deal, which demands serious preparation. But just how prepared is the drug development industry?

"There's an abundance of information out there about the consequences of no deal and I do believe that most companies in the clinical development space are prepared and have contingency plans in place," says Hegwood. "But there are no guarantees. Recently our couriers have had to put some destinations on hold because they couldn't land their planes as a result of extreme weather in the US, for example. I do think the potential impact of sudden regulatory and trading changes could be huge, but I think I can speak for the entire clinical supply industry when I say that we will do everything humanly possible to make sure that we can get clinical shipments through the minefield created by a hard Brexit."

References

1. *EconPol, "Hard Brexit ahead: breaking the deadlock" (2019). Available at: https://bit.ly/2D1M9mr. Accessed February 2, 2019.*
2. *J Strachan, "Hold Me Closer, UK Pharma", The Medicine Maker (2018). Available at: https://bit.ly/2GpCs4k.*
3. *Department of Health & Social Care, "How medicines, medical devices and clinical trials would be regulated if there's no Brexit deal" (2019). Available at: https://bit.ly/2o0lnUq. Accessed February 2, 2019.*
4. *Department of Health & Social Care, "EU Exit – Human medicines supply in a March 2019 'no deal' scenario: An update" (2019). Available at: https://bit.ly/2UGkGhq. Accessed February 2, 2019.*
5. *The National Archives, "The Human Medicines (Amendment) Regulations 2019" (2019). Available: https://bit.ly/2DpMUHi. Accessed February 2, 2019.*
6. *HM Revenue & Customs, "Register for simplified import procedures if the UK leaves the EU without a deal" (2019). Available at: https://bit.ly/2DSY4o6. Accessed February 2, 2019.*

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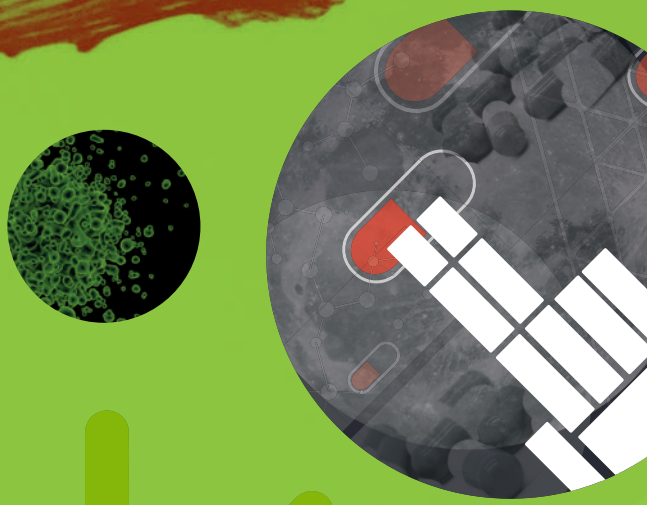

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The (Secret) Barrier Breaker

Sitting Down With… Steve Arlington, President at the Pistoia Alliance.

How did your career in pharma begin?
I had always wanted to become a doctor. But no plan runs true to course – much to my mother's relief. She always said it was divine intervention and a blessed relief to the human race that my medical ambitions didn't come to fruition, as I wasn't made to look after the sick! I got sucked into the world of immunology while studying at the University of Birmingham. By the time I had finished my PhD, my attentions had turned towards research and it was a case of serendipity that Smith, Kline and French (SK&F) had been looking for an immunologist who understood the effect of drugs on the immune system, as well as their role in blood disorders. At the time the company was small, but was working on big projects that would propel it into international acclaim.

What were your early achievements?
When I joined SK&F in the late 1970s, they were working on the world's first blockbuster drug, cimetidine, a drug used to inhibit stomach acid production. And while I can't claim any credit for the launch of the drug, I was fortunate enough to be a part of the company during its formative years and see many successful products sent to market. I was part of the team that launched Clearblue in 1985 and Clearblue One Step in 1988. They were massive technological breakthroughs and it is amazing to think that they are still highly recognizable products. And though I've never helped a patient in a hospital setting directly, I've been able to touch the lives of many through the products I've helped bring to market. Perhaps I'm not as bad at helping the sick as my mother thought!

What led you to the Pistoia Alliance?
As I was approaching the ripe old age of 60, I was working for PricewaterhouseCoopers, where partners retire at 60. Things were going well but I didn't want to spend my last year there with people waiting for me to retire! I decided that I would start a portfolio career. I wanted to give something back to the industry and sit on the boards of startup companies and support R&D. And then John Wise from the Pistoia Alliance operations team asked me to apply to the Pistoia Alliance board for the position of President. He was very persistent! And I thought it would be a challenging, interesting role because I'd need to convince people that they had to collaborate in a completely open structure. I'd have no power to force them to collaborate – I'd have to convince them through goodwill and influence.

What exactly does the Pistoia Alliance do?
I've become quite famous for saying that the Pistoia Alliance is one of the industry's best-kept secrets. It seems as though people are at opposite ends of the spectrum when it comes to the organization – they either know us well or have no clue! The people who know of the organization admire what we stand for and are willing to get involved with our initiatives, but I guess they must want to a keep a good thing to themselves…

The Pistoia Alliance is a global non-profit organization committed to forming collaborations between life science companies, technology and service providers, publishers and academic groups. We're all working together to increase innovation and lower the barriers in R&D. We consider our members to be equals in the projects they participate in because they are generating data that is of significant value to the worldwide life sciences community and should result in better healthcare for all.

Though the role has presented its challenges, the growth we've seen over the course of the last four years has been enormous. The success of our projects has done a lot to help industry players from academia and industry join forces and move the industry into new areas.

What's your focus for 2019?
If Brexit doesn't make the world fall apart, I'm quite certain that 2019 will be a positive year for the Pistoia Alliance. Of course, there will be some additional challenges because we're trying to forecast what the next decade will look like for the pharmaceutical and healthcare sectors.

"If Brexit doesn't make the world fall apart, I'm quite certain that 2019 will be a positive year for the Pistoia Alliance."

We've recently developed a life sciences innovation report with Clarivate Analytics to help identify the emerging trends driving innovation in the R&D industry. The data-driven report assesses the companies and academic institutions who have drugs in the pipeline and puts forward a list of the top 30 molecules and innovative products based on the data collected.

Our Center of Excellence in Artificial Intelligence and Machine Learning (AI/ML) is another pursuit we're very excited about. For years, AL/ML was only accessible to an elite group of specialists but we're now entering an era where its applications are more widespread than ever before. And though AL/MI has the capability to provide solutions within the life science space, regulatory approval will make all the difference when it comes to how well these technologies permeate the industry and influence innovation.

Most importantly as we move into 2019, we remind ourselves of the continued need to better understand all of our members so that we can break down even more barriers in the world of R&D.

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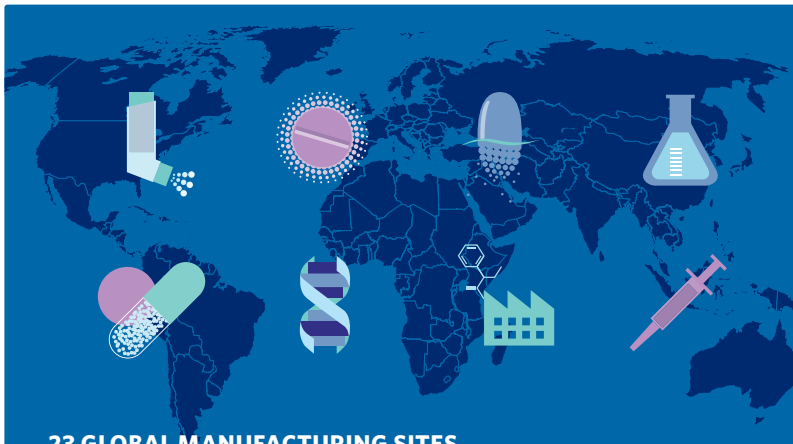

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