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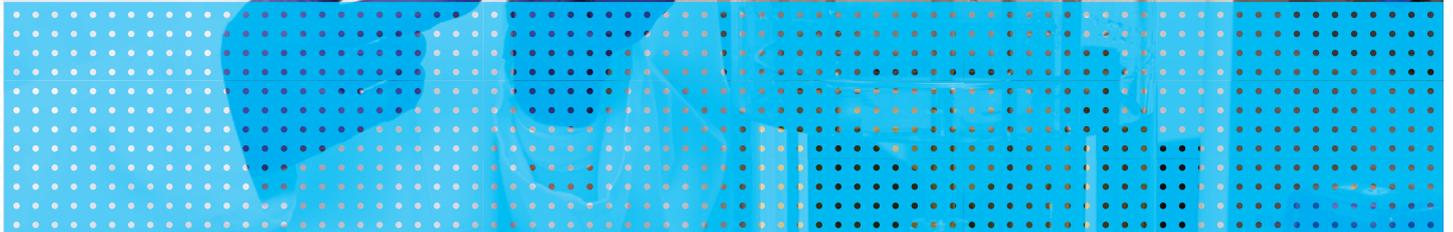
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Online this Month



I, Robot

First scientists created Adam, a robot capable of autonomously discovering new scientific knowledge. And now they have created Eve, a new robot that the creators hope will aid drug discovery, particularly in the area of neglected tropical diseases. “Standard ‘brute-force’ automated screening is simple to automate, but slow and wasteful of resources as every compound in the library is tested,” says Ross King, a professor at the Manchester Institute of Biotechnology.

Find out at tmm.txp.to/eve how Eve automates library-screening, hit-confirmation, and lead generation.

You've Got the Power

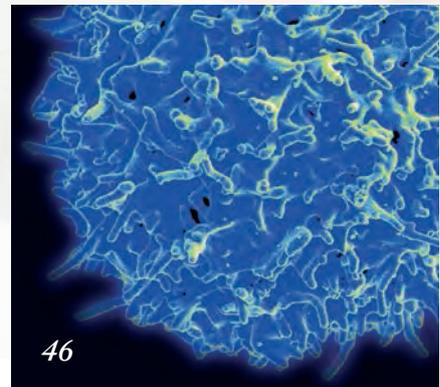
The Medicine Maker 2015 Power List is open for nominations! The list will rank the Top 100 most influential people in the industry, as chosen by you, the readers. Who are the role models and thought leaders in pharma and biotech, inspiring change in drug development and manufacture? A company CEO? A researcher? A philanthropist? A regulatory official? Perhaps even one of our authors? Whose name do you want to see on the list?

Visit tmm.txp.to/2015-powerlist or email charlotte.barker@texerepublishing.com to nominate.





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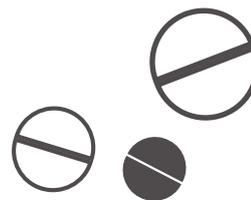
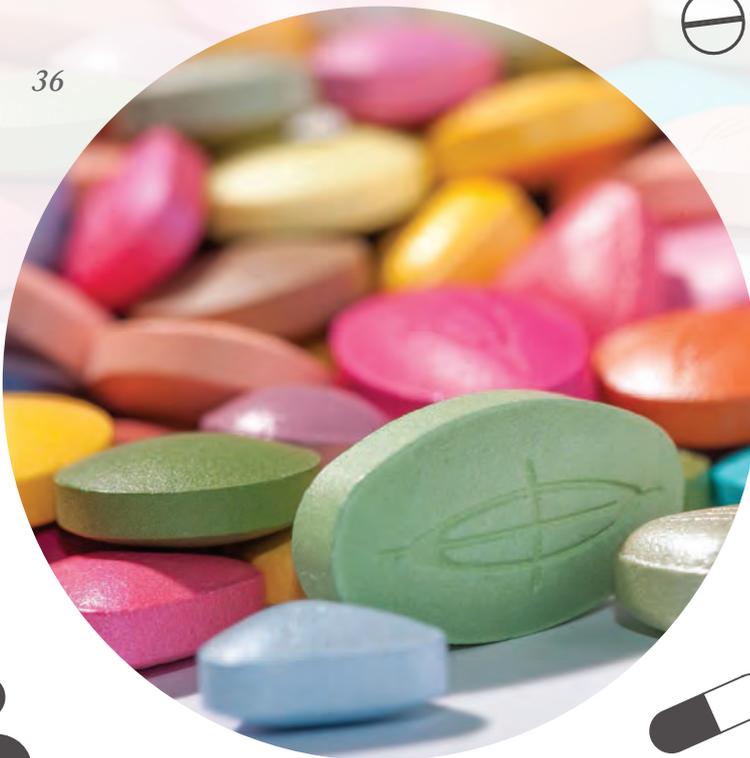
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Collaboration within companies is clearly vital, and these days big pharma working with biotechs is a given. Pharma companies have a long history of partnering with academia too – on page 10, University of California professor Greg Weiss reports that he has already had a number of calls from companies wanting to explore the exciting technology he has developed.

Unsurprisingly, collaboration between rival companies is much less common. However, in “Meet The Green Team” on page 23, green chemistry consultant Andy Wells draws attention to the “remarkable” increase in pre-competitive industry collaboration over the past 10 years. Why? To find leaner, greener manufacturing strategies. As well as joining forces on sustainability initiatives, companies have been collaborating on large-scale R&D projects (1) and working together to help develop new licensing pathways (2).

Collaboration – or at least meaningful collaboration – is by no means easy. Historically, pharma has had a propriety culture, not well suited to sharing knowledge. Many big pharma companies still struggle to be team players. A recent survey of biotechs shows the perceived ‘partnering skills’ of top drug companies lagging well behind their technical capabilities (3). If the biotech–big pharma relationship, with its clear benefits for both sides, can be difficult to manage, partnerships between rivals are harder still. Like a marriage, a good partnership requires hard work and compromise from all parties.

Ultimately, increased collaboration may be a necessity rather than a choice. The days of big pharma profits generated solely by in-house R&D are long gone, and perhaps that’s no bad thing. Done right, collaboration allows us to become more than the sum of our parts. It broadens our horizons, helping us look beyond the obvious to see new and creative solutions. In fact, what if we stepped outside the limits of the pharma industry altogether? GlaxoSmithKline did just that when forming a partnership with Formula 1 team McLaren. An odd combination? Not really. McLaren can replace all four tires on a racecar in four seconds – imagine the savings if pharma manufacturing could harness that efficiency.

There is no doubt that pharma companies can collaborate successfully. During World War Two, US and UK drug makers formed government-backed coalitions to scale up manufacturing of penicillin, saving countless lives on both sides of the Atlantic (4). Today, as well as conflict and disease, we’re facing new challenges caused by our reckless use of resources. If we can harness the collective brainpower, skill and commitment of this industry towards solving the world’s problems, we will all benefit.

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Charlotte Barker
Editor



Claire Thompson

When Claire was five years old, her father taught her how to play football. He said, “The difference between an average footballer and an exceptional footballer is their ability to look up. They know where the ball is - they look up to see where the opposition is and pick out the next pass.” Claire has applied this advice throughout not only her football career (where she played at international level), but also in business. She now fast tracks nanotechnologies into products and profits, advising investors on how to pick the winning assets; innovators on looking up from the bench and getting to clinic or market; and large corporations on strategic acquisitions and entering new markets. Claire has a degree in Biochemistry from the University of St. Andrews and a PhD from the School of Pharmacy, University of Nottingham.

Claire asks if nanotechnology can pick up where personalized medicine leaves off on page 16.



Andy Wells

Andy Wells started his scientific journey as an industrial analytical chemist, moving into the synthesis of organophosphorus ligands and novel organometallics for his PhD, then into the synthesis of pharmaceuticals. He has worked both within industry and in the consulting business, and collaborated with a number of leaders in green chemistry and sustainable manufacturing looking to bring new medicines to patients whilst minimizing any environmental impact. Commenting on changing attitudes to green chemistry, Andy says, “When I finished my PhD in 1985, green chemistry as a concept was unheard of, moving to a quirky and niche area in the mid-1990’s, and now business-as-usual for several big pharma companies.”

Pharma’s increasing focus on sustainability is explored by Andy and the rest of The Green Team on page 22.



Charlotte Miller

Charlotte went to work for GlaxoSmithKline as a Quality Assurance Clerk straight out of secondary school. She says, “The job was temporary and with dreams of becoming an artist I intended this to be a summer job before beginning my Art Degree. Fast forward 15 years and I’m still working in the industry – and I’m so glad I never made it to Art College.” Charlotte currently works as a tablet design specialist at Colorcon, where she gets to combine her natural love of art and creativity with technical knowledge. She has recently graduated as a mature student with a BSc in Biosciences. “I’ve been involved with so many unique and interesting projects. The best part of my job is meeting and assisting customers, which keeps me up to date with what’s really going on in the industry.”

On page 36, Charlotte takes us into the colorful world of tablet design



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Upfront

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

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

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How Do You Like Your Eggs?

Scientists in California have ‘unboiled’ an egg – with some interesting implications for biopharma...

A recent paper revealed a new way to ‘unboil’ egg whites (1), capturing the attention of the popular media – and *The Medicine Maker* – in the process. So, how did this remarkable feat come about?

A common problem in labs working with proteins is that newly synthesized chains bind to each other and become tangled, forming a messy protein aggregate. “This drives us nuts,” says Gregory Weiss, lead author of the paper and professor at the University of California Irvine. “It’s been a problem since I was a graduate student and it’s still a problem today, 20 years later.”

The method for untangling the proteins hasn’t changed in that time either. The solid protein aggregate is dissolved in urea, which coats the protein chains and causes them to untangle – going from a gummy solid substance to a liquid. The urea is then slowly removed to allow the chains to re-form in the correct structure, a tedious process taking four or five days of valuable research time.

A trip to Australia two years ago presented Weiss with a potential solution. “I found myself in the office of a very creative synthetic chemist, Colin Raston, who was

telling me about a new machine he had invented: the vortex fluid device. He told me how he was able to use it to pull apart one atom-thick sheets of graphite to produce graphene.” It immediately struck Weiss that the vortex fluid device might work on proteins too and he asked Raston to send him one. “He packaged one up and a graduate student brought it over to my lab,” says Weiss.

“The only problem was that it looked exactly like a bomb, with wires sticking out and a clock-like controller, so we were a bit worried what airport security might think...” But the student and device arrived safely in Southern California and Weiss’s team went to work, “Within a month we were getting really exciting data, showing that we could get proteins to refold in record times.”

In the new process, the protein–urea solution is rapidly diluted into water, which would normally cause the protein chains to re-tangle; however, the vortex fluid device pulls the proteins away from each other, giving them space to refold into their natural configuration. Weiss and his team tried out the process, which takes minutes rather than days, on several different proteins and were delighted with the results. They decided to publish the work so others could benefit, which is where the egg came in.

“The cancer-associated proteins my lab works with are very different to most proteins that scientists are familiar with,” explains Weiss. “I realized that if we wanted to show the peer reviewers that we had a generalizable technique with the power to tackle really tough challenges, we needed to try it on a protein that everyone knows. A hard-boiled egg seemed the perfect model.” When an egg is boiled, the proteins become tangled and disordered – the team proved that a key component of the egg white, lysozyme, could be returned to its original configuration using the vortex fluid device.



While unboiling an egg may not be particularly useful in itself, the technique could have a huge range of potential applications. “From our initial work, it looks like the technique can be used on many proteins,” says Weiss. One avenue the team are keen to explore is in biopharma manufacturing. “Biologics often require exotic cell lines and special conditions to

make sure proteins fold correctly and don’t become tangled,” explains Weiss. “Instead of getting the cells to do all the hard work of correctly folding proteins, we could get the vortex fluid device to use mechanical energy to force the proteins to fold after the protein is expressed from the cell.” And that could mean more efficient production and consequently lower costs. “We’ve

already had some interesting calls from drug companies and we’re excited about the future,” says Weiss. *CB*

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Orphan Affordability

Research into rare diseases is on the rise, but are prices sustainable?

In January, we reported that the European Medicines Agency issued a record number of positive opinions (17) for medicines for rare diseases in 2014. And the same trend can be seen in the US; the FDA approved 41 new molecular entities – 17 of which were for rare diseases in 2014, the largest number since the Orphan Drug Act was first passed in 1983.

A recent white paper from GlobalData attempts to identify the reasons behind the industry’s newfound focus on orphan medicines (1). In short, it’s all about strategy.

“Developing orphan drugs not only makes strategic sense, but also financial sense,” says Adam Dion, a healthcare industry analyst at GlobalData. “There is a need for the industry to replenish its product pipeline and to more rapidly access commercialization revenues. Orphan medicines typically have lower clinical trial costs and other benefits, such as tax credits and waiver of user fees.” Manufacturers are also attracted by the high price commanded by orphan medicines. In December 2014, Amgen announced that its new acute

lymphoblastic leukemia drug (Blinicyto) would cost \$178,000 per year per patient. Alexion Pharmaceutical’s Soliris – the world’s most expensive drug – is also an orphan product. The monoclonal antibody drug approved for treating paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome costs \$409,500 in the US. In the UK, the drug was recently approved by the country’s healthcare cost watchdog, NICE, and will cost around £340,000 per patient per year.

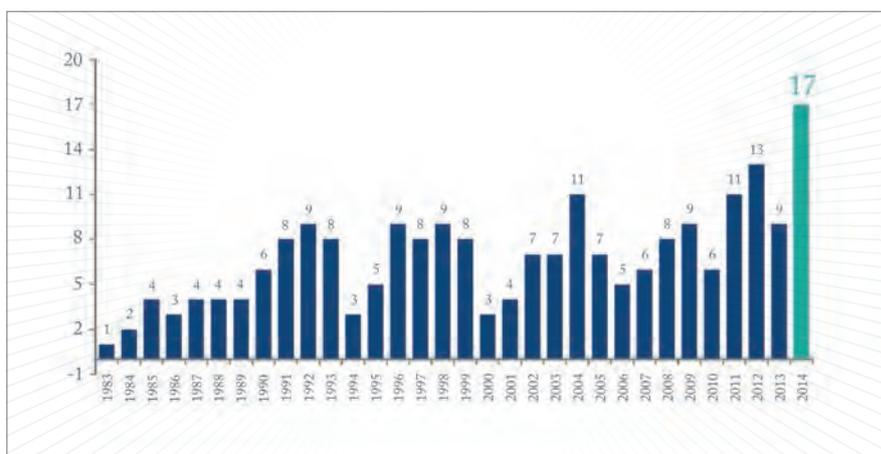
“Amgen has come under fire for the price of Blinicyto – it’s one of the most expensive cancer treatments,” says Dion. “Orphan drug affordability is now a big issue for payers and governments. Healthcare costs are exploding worldwide and there are some very difficult questions being asked

about whether the prices of orphan drugs are justifiable or even sustainable in the long term.”

For the moment, however, the white paper acknowledges that there are financial gains for companies involved in developing and commercializing orphan medicines. In a peer group analysis of sales data for 50 orphan drugs, the paper estimated combined sales in 2013 at around \$48 billion. This is expected to reach almost \$90 billion in 2019. *SS*

Reference

1. GlobalData, “Drug Approvals Reveal an Industry Shift to Rare Diseases” (January, 2014), <http://healthcare.globaldata.com/resources/white-papers/drug-approvals-reveal-an-industry-shift-to-niche-diseases>



Number of orphan drugs approved, 1983–2014

Source: FDA Centre for Drug Evaluation And Research

Violation Without Intent?

The FDA is not impressed with data mishaps or missing petri dishes – however unintentional...

Generic drug maker Apotex has received several FDA Warning Letters in recent years, with the latest being sent at the end of January 2015 (1). The letter stems from an FDA inspection conducted in June/July 2014. Apotex has already responded to the FDA's inspection observations seven times, but the FDA is not satisfied with the replies or proposed corrective actions. In fact, the letter states that some of the explanations raise "further issues."

The problems noted in the Warning Letter relate to one of the company's plants in Bangalore, India, where there were issues in data integrity practices, including disregarding "trial" test results, missing test plates, and a lack of oversight over laboratory computer systems.



"Trial" sample testing was also noted in January 2014 during an FDA inspection of another Apotex plant in Bangalore. In the latest warning letter, the FDA says that the "inspection of your facility documented multiple incidents of performing 'trial' testing of samples, disregarding test results, and reporting only those results from additional tests conducted."

With FDA investigators noting instances where quality control personnel created unauthorized folders on laboratory computerized systems, the letter makes it clear that Apotex's response leaves much to be desired, "In correspondence with the Agency, you indicate that no malicious data integrity patterns and practices were found. Also, you state that no intentional activity to disguise, misrepresent or replace failing data with passing data was identified and no evidence of file deletion

or manipulation was found. Your response and comments focus primarily on the issue of intent, and do not adequately address the seriousness of the cGMP violations found during the inspection."

The company's investigation into a number of missing test plates also failed to impress the Agency. According to the letter, the company claims that "two analysts momentarily panicked" and removed the plates "in an utterly misguided and ill-conceived attempt to clean up the microbiology lab prior to the start of the FDA inspection."

Apotex is working with a third-party consultant to conduct a comprehensive audit of the company's systems and data integrity. *SS*

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Pfizer-Fueled Rumors

Could the Pfizer-Hospira deal be a stepping stone to a company split?

In early February, Pfizer announced that it would acquire Hospira for around \$17 billion. Hospira's shareholders are set to profit from the deal, with Pfizer paying \$90 per share, a 40 percent premium, and netting Hospira CEO F. Michael Ball an estimated \$80 million payout (1).

The merger will substantially boost

Pfizer's portfolio, particularly in the emerging biosimilars market. Especially given that a couple of weeks after the announcement, Hospira launched a generic version of J&J's Remicade (infiximab) in several European countries. The FDA will consider in March whether to approve the drug in the US.

The news has raised plenty of speculation in the pharmaceutical and business press. Most analysts agree that Pfizer is plotting further acquisitions in the coming months, with one article touting GlaxoSmithKline and Actavis as potential targets (2). The deal is also being seen by some, including David Crow at the Financial Times (3), as

another indication of a long-term plan to split Pfizer's generic and brand name portfolios into separate companies. A split has certainly been mentioned as a possibility by Pfizer CEO Ian Read in the past, but only time will tell. *CB*

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Good Things Come in Small Packages

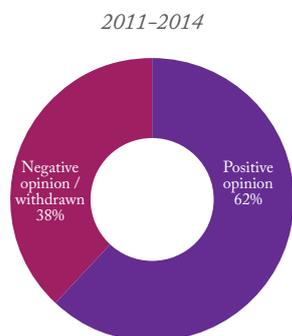
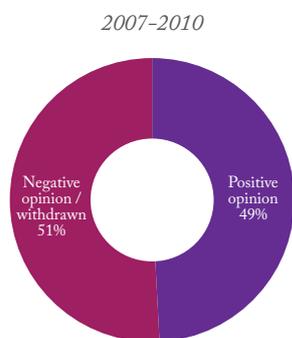
Is early and regular dialogue with regulatory agencies the key to success for smaller companies?

Increased uptake of the EMA's advisory services, including scientific advice during development and biomarker qualification, seems to have led to increased success rates for small and medium-sized enterprises (SMEs), according to the EMA's annual SME Report. The report notes, "Initiating dialogue early and repeating it at major milestones is important to decrease the quality and clinical failure rate at time of marketing authorization review." Notably, there are still areas for improvement, with quality and clinical documentation attracting the most objections – particularly in the biologics area. *CB*

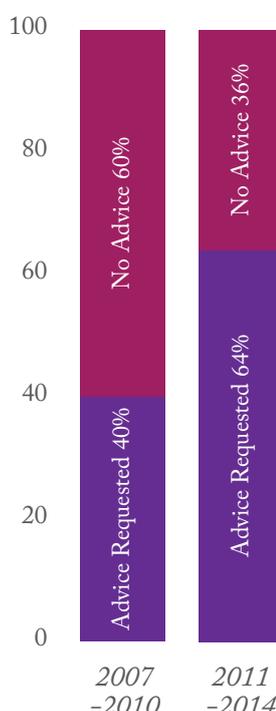
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SMEs REGISTERED
WITH THE EMA

45 SME
APPLICATIONS
IN 2011-2014

SME applications for marketing authorization



SMEs seeking EMA advice during development



Who Are the Most Powerful Medicine Makers?

Only you have the answer. Nominate now.

Nominations are open now for The Medicine Maker Power List 2015. The list will celebrate the Top 100 most influential people in pharma development and manufacturing, based on our readers' nominations. It's proving to be a hotly contested race, with so many great leaders, engineers, scientists and educators in the running.

As well as being an entertaining feature, the Power List has a deeper purpose – to celebrate the achievements of an often self-deprecating field. With that in mind, we encourage you to nominate opinion leaders from pharma, biopharma, academia, SMEs, CMOs, or government, from all over the globe.

The nominations will be whittled down by our international judging panel and all those who make the Top 100 will be featured in print and online in The Medicine Maker. Do you have a colleague or mentor who deserves recognition from their peers? Whether you are a CEO or toiling away at the coalface, it's nice to be recognized. Take a minute to nominate someone you admire and help us highlight the people who are making a difference.

Nominate online at tmm.txp.to/2015-powerlist or email charlotte.barker@texerepublishing.com.

Better, Faster, CRISPR

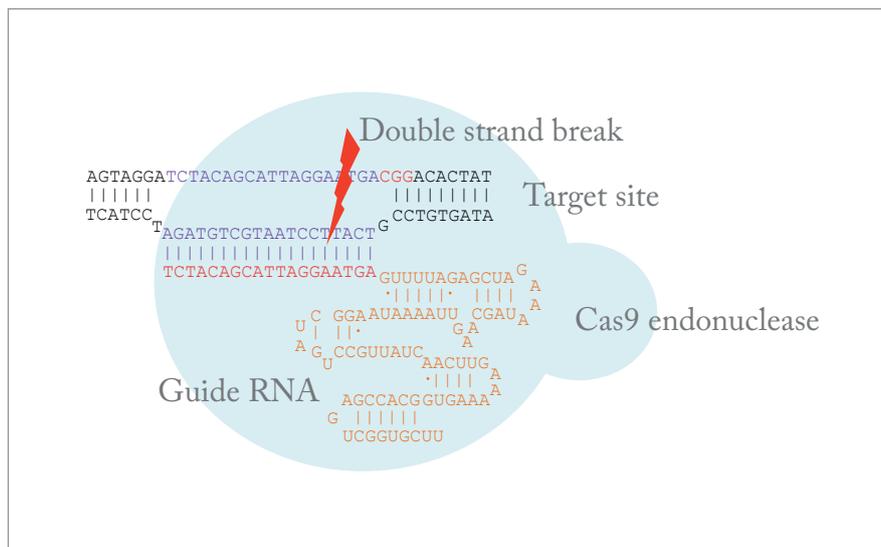
Pharma companies look to new genetic screening technology to enhance drug discovery

Clustered regularly interspaced short palindromic repeats (better known as CRISPR) has caused quite a stir in the scientific research community. Essentially, it allows precise genetic changes to be made and its potential as a drug discovery tool has not gone unnoticed by pharma companies. Novartis signed off a CRISPR deal at the end of January and now AstraZeneca has announced its own CRISPR research project; the company will collaborate with four research partners (Wellcome Trust Sanger Institute, the Innovative Genomics Initiative, Thermo Fisher Scientific and the Broad Institute/Whitehead Institute) to use CRISPR to identify and validate new drug targets in preclinical models in certain therapeutic areas. It's an open innovation project, which means the findings will be shared between the research partners and published in peer-reviewed journals.

We spoke with Kosuke Yusa, a member of the Sanger Institute Faculty, to find out why we're likely to see CRISPR in more pharma discovery labs in the future.

How does CRISPR work and why is it so exciting?

It has been known since the early 1990s that DNA double-strand breaks (DSBs) in mammalian cells are recombinogenic and that it is possible to edit the genome using the endogenous DSB repair machinery. However, there was no technology at the time that allowed us to induce DSBs at a specific site in the genome. The CRISPR-Cas system is a new technology consisting of two components: a guide RNA and a Cas9 endonuclease. They form a



Mechanism of CRISPR

ribonucleoprotein complex and induce a DSB to the genomic site determined by the guide RNA. The system is incredibly simple compared to other gene-editing technologies. We can generate a new reagent for the CRISPR-Cas9 system in less than a week at the cost of only a few dollars.

How exactly can it help drug discovery? RNAi screens have been a powerful means to drug discovery, but they require a large initial investment and considerable running costs; typically, results from a limited number of test subjects (usually just one cell line) are used to identify new drug targets. CRISPR screens are cheaper and more scalable. Multiple samples can be tested, which will allow us to comprehensively identify drug targets. Pharmaceutical companies can also use CRISPR to generate reporter systems to measure the efficacy of candidate drugs.

How did the collaboration with AstraZeneca get started?

When we published our paper describing CRISPR-based genetic screens in *Nature Biotechnology* (1), I received an email from my current collaborator in AstraZeneca mentioning another potential collaboration using our technology for drug discovery. Subsequently, we had several meetings and discussed potential projects. We are now in the process of

recruiting two postdoctoral scientists who will work on the project.

How successful has CRISPR been so far? Success stories to date are centred around technology development. One particular example is in vivo genome editing. A paper published in *Nature Biotechnology* last year (2) showed that a mutation was reversed into wildtype and mice suffering from a gene defect were completely cured. The paper showed the potential of CRISPR as a therapeutic agent.

What's the future of CRISPR?

As a tool for genome-wide mutagenesis, CRISPR is more than perfect as it is, in my opinion. As a tool for genome editing, there have been a number of techniques developed. There will be some refinement to increase overall efficiency of genome editing, but the current form of the technology is efficient enough for most applications. In the next couple of years, CRISPR will become a routine technique, like PCR, and there will be many new discoveries. *SS*

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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 editors at edit@texerepublishing.com

A Personal Question

Can nanotechnology pick up where personalized medicine leaves off?

By Claire Thompson, Director, Nanoscientium, London, UK.



Personalized, precision or stratified medicine – we can't agree on what to call it but we all agree that we desperately need it. With even the most promising modern medicines showing therapeutic activity in only around 30 percent of the population (1), we need to get better at predicting, detecting and targeting diseases across populations.

There is no shortage of international initiatives and funding to fuel innovation in this area. For example, in January 2015, US President Barack Obama launched a Precision Medicine Initiative, while in the UK the 100,000 Genomes Project is already well underway. These programs will lead to a much greater understanding of the diversity of our genomic make up and a plethora of new targets for drug development or diagnostics.

But this is where the current remit of personalized, precision and stratified medicine tails off, and we need to go further. For medicine to be truly personalized, we cannot simply become better at predicting disease. We must be able to routinely and reliably detect, monitor and target disease, and this is where nanotechnology comes to the fore.

Nanoparticles or nanocomplexes are already routinely used in diagnostics.

From pregnancy testing to malaria diagnosis, they enable precise, accurate and reproducible data. Rather than medical professionals taking blood samples and sending them for analysis off-site, we are starting to see more point of care diagnostics, where nanosensors allow rapid readout from small samples. Nanotechnology is also used in diagnostic imaging. For example, EndoMag has developed a handheld magnetic probe (SentiMag) and magnetic tracer (Sienna+) to localize lymph nodes for cancer detection and staging. The products will be launched in the US in 2015.

The Qualcomm Tricorder X Prize is catalyzing the convergence of PoC diagnostics with digital or e-health. The prize professes to be “turning science fiction into reality” and who would argue with them? It is a global competition to make a portable device that can diagnose 20 different medical conditions and readout continuously to “put healthcare in the palm of your hand”. The top 10 teams, including teams from the US, Canada, India, Taiwan, Slovenia and the UK, all use nanosensors.

The biggest issue with delivering precision medicine is exactly that – delivery. Targeting drug molecules to the right organ, tissue or cell is an

“We must be able to routinely and reliably detect, monitor and target disease, and this is where nanotechnology comes to the fore.”

ever-present problem in pharma and biotech. Nanotechnology from BIND Therapeutics is helping to overcome this challenge. Founded by Professor Robert Langer from Massachusetts Institute of Technology, BIND's flagship technology, Accurins, deliver targeted and programmable therapeutics. Accurins are functionalized nanocomplexes that target disease-specific cells or tissues and deliver their therapeutic payload directly to the site of disease. Such targeting enhances efficacy and minimizes adverse effects on healthy tissues. BIND has already demonstrated positive Phase II results for non-small cell lung cancer and has inked deals with Amgen, Pfizer, AstraZeneca, Roche and Merck.

The field of theranostics, which combines diagnostic and therapeutic capabilities into a single agent, is another emerging technology, with the potential to diagnose and deliver the right dose to the right tissue at the right time.

Personalized medicine doesn't just relate to genomic subsets of a population – targeting drug delivery to specific age groups can also make a big difference to patients. For instance, VaccineTab has developed a liposome-encapsulated nanotechnology for vaccine delivery. It is a needle- and pain-free delivery system, so it has particular benefits for children's vaccinations. In addition, the VaccineTab technology is thermally stable, thus reducing the need for cold

chain product supply. In the developing world, where the cost of vaccines and lack of cold chain logistics prevent effective vaccination programs, VaccineTab could have a huge impact.

With its health market predicted to reach US\$1 trillion by 2021, it is abundantly clear that nanotechnology will pick up where genomics ends, driving disease detection and the targeted delivery of personalized medicine. They do say that good things come in small packages...

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Classifying Manufacture

A classification system could make the R&D-manufacturing interface much easier to navigate.



By Michael Leane, Principal Scientist, Bristol-Myers Squibb, Moreton, UK.

Why do I think we need a manufacturing classification system (MCS) for pharmaceutical development of oral solid dosage forms? Simple: the timing is right. There is an increasing focus on simplifying development, identifying risk and using knowledge to design better processes that will increase robustness, improve speed of delivery to

patient and reduce costly failures.

The pharmaceutical industry already has a relevant example: the Biopharmaceutics Classification System (BCS), a scientific framework for classifying the in vivo absorption risk of drugs based on their solubility and permeability. The BCS allows rapid assessment of project risk and directs effort towards the appropriate areas. Given the success of the BCS in the biopharmaceutical area, a team within the Academy of Pharmaceutical Sciences (APS) decided to explore whether an MCS to aid drug product manufacture would be useful. The driver was the awareness that many aspects of the current situation are not ideal. There is no definition of what the “right particles” are and what the “best process” is, which leads to a lack of clarity in the goal for particle engineering efforts. By providing a common understanding of risk, an MCS could predict from prior experience and reduce the potential for issues across the key interface between R&D and manufacturing.

At a subsequent seminar to consider this initiative, there was a large degree

“There is no definition of what the ‘right particles’ are and what the ‘best process’ is, which leads to a lack of clarity in the goal for particle engineering efforts.”

of enthusiasm and great input from the delegates present – and even a pleasing degree of agreement on the basic structure: an MCS based on processing routes divided into four classes:

1. direct compression
2. dry granulation
3. wet granulation
4. other technologies.

The structure assumes that there is a preference for simpler manufacturing routes. Moving down through the classes, process complexity increases, increasing cost of goods and the risk of unwanted changes to the API. In the case of wet granulation, for example, addition of water along with drying and milling steps could lead to undesirable form changes, API attrition, and degradation.

Having established the structure, the next step is to determine what API properties are important when selecting or modifying materials to enable an efficient and robust pharmaceutical manufacturing process. I believe that most formulators already have an informal MCS in their own heads. It's what comes to mind when someone approaches you for advice on a new project. What questions do you ask to rapidly assess risk? BCS Class? Dose?

Likely drug loading? I would certainly ask all those questions, and, in addition, I always like to examine the size and shape of a new API under a microscope. I have found that higher-risk APIs tend to be smaller and more needle-like. What's in your mental MCS?

I will not give a detailed technical overview of our progress so far here, as it can be found in our recently published white paper (1), which also gives examples of an ideal direct compression material, properties necessary for dry and wet granulation, along with examples of when other technologies may be needed. Once you have read the white paper, we would be interested in hearing your opinions and suggestions. You can contact us by email (MCS@apsgb.org), by participating in our conference roundtable session at FIP 2015 or by completing our online survey

(<http://tmm.txp.to/0215/MCS>).

A working group has now been established with the aim of publishing a second, more detailed white paper that could involve gathering more data on input API, possibly in a centralized database. It will also consider the use of target material profiles, which would inform API optimization. Identification of surrogate materials that could act as model materials for each MCS class could also be a promising route forward along with the development of modeling tools for predicting formulation performance. If you think you can contribute, then please get involved.

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Women on the Verge of a Clinical Breakthrough

Women's health used to be considered solely in terms of maternal and reproductive health. Not anymore. As our knowledge of the basic biological differences between the sexes grows, it's clear we must take action to ensure women are represented throughout the drug development process.

By Phyllis Greenberger, President and CEO of the Society for Women's Health Research, Washington, DC, USA.



Traditionally, women – and particularly women from ethnic minorities – have been under-represented in clinical trials. Until relatively recently, the prevailing belief was that a medicine could be tested on white men and would work similarly in everyone else. We now know that is not the case, and despite efforts from regulators and advocacy groups over the past decade, change has been slow.

We are really only now beginning to understand some of the differences between men and women, and a lot of the findings are still from basic research – differences in neurology or gastroenterology. Right now, we have the most information on cardiovascular

“It's been a long time coming, but we've certainly seen some major progress in the last year.”

disease but even in this field there are still many unanswered questions, such as why certain treatments work better or worse in women, or why women suffer more in certain aspects of cardiovascular disease than men. We know that there are differences in many areas in terms of prevalence and symptoms, but in most cases we don't know why. Does a specific treatment work in one sex and not the other? Do men and women require a different dosage? We seem to have many

“Does a specific treatment work in one sex and not the other? Do men and women require a different dosage? We seem to have many more questions than answers.”

more questions than answers. We need to bring research to the bedside and test hypotheses.

For years, my colleagues and I at the Society for Women's Health Research have been calling for more women to be included in Phase I and II trials. Women are all too often only included in Phase III trials, after initial safety and efficacy analyses have been completed. There are barriers; for example, women still take on the majority of child rearing and caring for elderly relatives, making long stays or frequent trips to trial centers challenging. And, there are a range of social and cultural issues that further reduce participation from ethnic minorities. There is still mistrust among the African-American community after infamous incidents like the Tuskegee trials, where life-saving treatment was deliberately withheld from African-American trial participants at the cost of many lives.

The aim is not to increase participation of women to 50 percent in all trials, but to achieve statistically significant, clinically balanced representation. If you're designing a trial for Lupus, which is eight times more prevalent in women than in

men, then ideally your study population should be predominantly women.

Recruitment is just the beginning; you also have to analyze your results to look for sex or ethnicity differences. Why is there a 40 percent failure rate and, crucially, in which patients? Hypotheses about the impact of sex and ethnicity need to be considered at the beginning of the trial (not afterwards) to ensure that analyses are statistically significant. The FDA has been active in encouraging this approach. Its new Drug Trials Snapshots provide information on age, race, and sex of clinical trial participants for a drug, and will put more pressure on companies to make sure they have the right data.

It's not just clinical trials where we need to see more female representation. Beginning this year, all preclinical studies funded by the National Institutes of Health are required to take account of sex differences in the cells or animals being used. It's a big change in thinking for a lot of researchers and it will introduce some extra costs and complexity, so it's going to be a slow process. But ultimately it's the only way we can unravel the full complexity of sex differences, “from womb to tomb”.

It's been a long time coming, but we've certainly seen some major progress in the last year. I believe that if regulators continue to make trial participation more transparent, the public is going to demand greater inclusion of women and minorities in clinical trials. The test for pharmaceutical companies will be how they respond to that demand. Doing what we have always done is no longer an option – we must close the gaps in our knowledge. We must achieve the levels of participation in clinical trials that are necessary to understand the biomedical differences between men and women. This will truly lead to our overarching goal – ensuring that the right patient, receives the right treatment at the right time.

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Who's Developing Your Process?

Cutting corners in process development will come back to haunt you – especially in the biopharmaceutical arena.



By Jan Gunnar Gustafsson, Bio Evaluation BO AB, Uppsala, Sweden.

Once upon a time in the pharma industry everything revolved around small molecules. Small molecules are manufactured by chemical engineers and overall, the compound can be well characterized and the structure analyzed with a high degree of precision. Though this isn't a simple task, people who are skilled in the art can design and control the production so that it meets industrial manufacturing requirements.

But in the 1980s, biopharmaceutical molecules burst onto the market, and added a whole new layer of complexity. Biologics are not nearly so easy to develop and manufacture, and require expertise in biochemistry, microbiology and molecular biology. Living organisms do not always behave as we want them to, when we want them to. Potential problems abound; the amount of product might be tiny or unwanted compounds (sometimes toxic) might be produced. Most companies weren't equipped to deal with these new types of products. Some started to build new capabilities in house, but many looked to contract manufacturing organization to do it

instead. Companies that didn't build their own facilities also didn't build their own in-house know-how and expertise for working with biopharmaceuticals.

Outsourcing is not inherently bad, of course, and has many advantages, but it can mean that process development is sometimes rather neglected. In my view, there isn't much interest in being a pharmaceutical company that researches, develops and manufactures all of its own products in-house in today's industry. Instead, every company has their own strengths. Big pharma excels at commercial manufacturing, marketing and selling, and is less adept at research and process development. Small companies often focus on research, hoping to sell their fledgling products on to big pharma once proof of concept has been demonstrated. These small companies don't have the money or resources to do the process development either. Some medium-size companies do have process development in-house, but those companies also tend to have many projects on-the-go at once. It's difficult to be an expert in process development for all of your products, which poses a problem as many big pharma companies now refuse to buy an investigational drug until the process development has been completed. Biotechs with a great idea but limited process development can increasingly expect to hear statements such as, "We like your project. Come back to us when you have a good process for it and then we'll buy it."

So who is going to do the process development? Most will turn to a contract manufacturing organization (CMO). It is at this point that the lack of in-house knowledge can create a few problems. When a project is outsourced, it's up to the customer to give the CMO clear guidance on expectations and outcomes. If you lack process development expertise, that

"It's tempting to push CMOs for the lowest price. But when people try to save money, they often cut corners."

communication can be difficult since you may not know what you want or what you'll need to sell the idea to big pharma. And when the CMO develops the process, it may be difficult to assess its suitability. One way to overcome these issues is to hire a consultant, who can bridge the knowledge gap and make sure that you get what you need.

It's tempting to push CMOs for the lowest price. But when people try to save money, they often cut corners. You may find that an underpaid CMO doesn't do all the activity that is really needed to develop a well-controlled process. Indeed, you may end up with a process that will work on a good day but not a normal day – let alone a bad one.

Even though there have been enormous improvements in analytical tools for biomolecules, their accuracy is not comparable to that of small molecules and there are many things that can go wrong in biotech development and production. If you don't have the expertise in-house then you must take help from someone who does. But please be warned – do not cut corners. Choose CMOs and consultants who you trust to give you honest advice, not just the lowest price. Whether you outsource or build expertise in-house, it is crucial to invest in process development if you want to give your product – and your business – the best chance to of success.

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MEET THE GREEN TEAM



Pushing for cleaner, greener manufacturing is not only good for the planet, it's great for business. But it's not a task that can be accomplished by one company or organization alone – only by learning from each other will we achieve a more sustainable future.

By Andy Wells

Why should modern medicine makers engage with green chemistry and environmental sustainability? Compliance with existing environmental legislation is a given, but we also need to look at what's around the corner. Products are increasingly being scrutinized by shareholders and stakeholders alike in terms of green credentials like carbon footprint and environmental fate. The industry will be held to ever-higher standards in terms of our impact on society and the natural world.

But it's more than being a good corporate citizen. Greener and more sustainable manufacturing means the elimination of hazardous and environmentally damaging materials, lower usage of input materials, reagents and solvents, so less demand on natural resources and less waste to dispose of at the end of the process. This should simplify supply chains and lower costs – it's good business sense.

In moving towards more sustainable pharmaceutical manufacturing, we need to develop and adopt new science and technology, but new processes and equipment aren't the only way for us to make progress. We also need to pay close attention to the following crucial areas.

First, training and education are vital – not just for current staff, but also for the students who will be the next generation of employees. Everyone should be engaged in the greener manufacturing agenda, from the CEO to the newest recruit in the lab.

Second, we need appropriate tools and metrics to measure and quantitate progress – we need to ensure we are not deceived by a focus on single-issue sustainability, but instead look holistically at the complete process.

Third, industry needs to work with academia to translate important new scientific discoveries to a point where they can be quickly adopted by industry. It's all too common to see an exciting new catalyst or chemical transformation be developed, only to find that it will only work in a solvent that is completely unsuitable in a manufacturing environment. We desperately need new ways to conduct highly translational

research to make sure scale up is on the agenda from the start.

Fourth, as we move forward, new and improved toolboxes for industrial biotechnology and synthetic biology will become available alongside innovative engineering solutions. The winners in the sustainability game will have the philosophy and capability to work effectively at the interface of chemistry, engineering and biotechnology.

For me, the key to accelerate and quickly embed green chemistry and more sustainable pharmaceutical manufacturing is collaboration. It is remarkable how the pharmaceutical industry has moved over the past 10 years or so to work in a more collaborative way across a number of non-competitive areas – green chemistry being a prime example. Some exemplars of industry–industry and industry–academic collaborations include the IMI public–private partnership CHEM21 featured in this article, the ACS GREEN Chemical Institute Pharmaceutical Roundtable, and the Centre of Excellence in Biocatalysis, Biotransformations and Biocatalytic Manufacture. I am proud to have been associated with all of these collaborations, and believe that they have delivered – and will continue to deliver – a great deal of value to the pharmaceutical industry and, ultimately, back to stakeholders and patients.

Some companies have already come a long way, while others are just starting their green manufacturing journey. There is still some distance to go to really embed green chemistry and environmental sustainability in the global pharmaceutical industry. Serious improvements are still needed in solvent selection and use in the global arena, and there needs to be a big focus on stopping the outsourcing of environmentally damaging processes to low-cost manufacturing in Asia and the Far East. However, there are many excellent examples of good practice out there that we all can learn from and build on. Here, we recognize some of the organizations and initiatives leading the way to a greener future.

Andy Wells is Managing Director and CSO of Charnwood Technical Consulting, UK.

Chemical Alliances

A multimillion Euro project is pushing green chemistry forward in Europe. The secret of its success? Collaboration, collaboration, collaboration! CHEM21 is a €26 (\$29) million project that brings together European pharmaceutical companies, universities and small to medium enterprises to develop more sustainable pharmaceutical manufacturing.

The project launched in 2012, after successfully bidding for funding from Europe's Innovative Medicines Initiative. The companies involved – members of the European Federation of Pharmaceutical Industries and Associations (EFPIA) – had for several years felt that there were gaps in their manufacturing technology portfolio. Promising technology to improve sustainability was being explored in academic labs, but was not yet available for large-scale use. Some members are also looking to utilize any new chemistry developed in drug discovery programs.

CHEM21 accelerates the development of sustainable technology with five working groups:

1. Horizon scanning: examines where we are now and where we might be 5 or 10 years in the future, to ensure that the technology being developed is relevant now and in the future.
2. Chemo- catalysis and flow processing: develops more sustainable chemical catalysts and processes.
3. Biocatalysts: identifies and refines novel biocatalysts to replace inefficient chemical catalysts.
4. Synthetic biology: uses microorganisms to transform simple carbon sources into high-value chemical intermediates.
5. Training and education: creates a world-class, interactive training package, which will open to the entire industry at the end of the project.

Project coordinator Nicholas Turner, a professor at the University of Manchester, is quick to point out that none of these elements works in isolation. “One thing that sets CHEM21 apart is the seamless integration of chemical and biological approaches to sustainable manufacturing.”

CHEM21 involves 21 different organizations. And while there is strength in numbers, working in such a large consortium can be challenging. “We are working on sensitive



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new chemical entities and drugs in development so there are sensitivities between the companies about exactly what we want to reveal to each other,” says project coordinator Murray Brown of GlaxoSmithKline. “It has also been important to remember that the academics are here to provide cutting edge research, not to be treated as contract research organizations, so they need to have trust that they aren't being exploited for commercial gain.” To alleviate any confidentiality concerns, the drugs for research projects are carefully chosen, with a focus on World Health Organization-defined Essential Medicines. “They are often part of a company's philanthropic portfolio, rather than their ‘crown jewels’”, says Brown. “Increasingly now we see people being prepared to share things that they might originally have been a bit nervous about. We are now very much a unified consortium, and I think that is a great achievement.”

The project has just passed the halfway mark of its four-year funding period, and much has been achieved already.



Translation Taster

Just a sample of the wide range of practical advances being developed as part of CHEM21.

1. C-H activation chemistry developed at Antwerp University is being applied to find a greener manufacturing route to GSK's anthelmintic drug albendazole.
2. Enzymatic routes are being identified to produce ethambutol, a key component of TB therapy.
3. A reaction database has been set up that allows researchers to assess how green a biocatalytic reaction is.
4. Direct fluorination, using elemental fluorine as the fluorinating agent, is being explored as a replacement for current approaches.
5. Research at the University of York is developing silica catalysts as cleaner alternatives to wasteful reagents used for amide bond formation.



academic partners have also addressed that missing link. “The toolbox has done a lot towards clarifying the complex IP landscape of synthetic biology and making it much easier for us to operate freely,” says Brown. “Now the challenge is to convert that toolbox into real industrial processes.”

Technology transfer is often a stumbling block in academic–industry collaborations, and CHEM21 is designed to make the process as easy as possible. Turner says that PhD students and post docs worked in close collaboration with industry staff from day one. “The best way to transfer technology is to transfer people, so we sent students off to work in industry for anything from a week to 2–3 months. We have also taken company staff into the academic labs for training. It’s all part of the exchange of information, technology and expertise.” GlaxoSmithKline have already felt the benefit of this close collaboration, adds Brown. “The consortium gives us the opportunity to work together to improve the process, whereas if we were just buying in technology from a third party supplier it would be much harder to have that level of interaction.”

Wells agrees, “I hope that this will become the model for how industry should collaborate with academia.”

As the project moves into the final two years, the focus will be increasingly on translating new technologies into economically viable processes, says Wells. “It’s very exciting to see the result of the research and the speed at which we are getting ground-breaking new science being picked up and used in real-life industrial examples.”

“We’ve now got a large portfolio of promising new technology, new catalysts, and new reactions that have come out of the academic partners. Companies are now looking at how they can use those technologies and some are already being scaled up. So we’ve gone from academic labs to industry labs and heading towards small-scale pilot plants in just two years,” says Andy Wells, Charnwood Technical Consulting.

Brown highlights the work on synthetic biology as one of the success stories of the project. Companies have long wanted to use genetic engineering to create microorganisms capable of producing valuable chemicals as a means for more efficient, sustainable manufacturing. What has been missing is a toolbox – a collection of techniques and technologies that companies can use ‘off the shelf’ to explore this potential (see January’s “Rebirth of Manufacturing” tmm.txp.to/rebirth). CHEM21

Find out more about the CHEM21 project at www.chem21.eu

How Green is Green?

By Frank Roschangar, Al Kurose, Roger A. Sheldon and
Chris H. Senanayake

The rapidly evolving field of green chemistry is concerned with minimization of waste and avoidance of toxic and hazardous substances in the production and application of chemical and pharmaceutical products. Why should the pharmaceutical industry in particular be interested in promoting green chemistry? We believe that the broad adoption of green chemistry principles as a core business strategy will increase the industry's sustainability and R&D productivity (1), and also bolster its reputation (2), in the context of rising healthcare costs combined with growing public awareness of high-profile environmental issues like global warming.

Strides have been made within the pharmaceutical industry to incorporate potentially disruptive green chemistry and engineering philosophies over the past two decades since the invention of the E-factor (3) and introduction of "The 12 Principles of Green Chemistry" (4), yet there are still a number of barriers to full adoption.

There is an old management adage that states, "You can't manage what you don't measure", and unfortunately the science of green chemistry does not have a standard measure for process 'greenness.' Instead, there has been a proliferation of green chemistry metrics over the past decade. E-factor and Process Mass Intensity are frontrunners, but no clear favorite has emerged. As such, green chemistry is perceived by some as a scientific curiosity with many 'soft' and non-quantifiable descriptors.

Another significant impediment to broad adoption of green chemistry is that we lack a clear definition of process starting points in the assessment of process greenness for the synthesis of active pharmaceutical ingredients (APIs). This has been a bothersome source of inconsistency in the literature. Failure to define an appropriate starting point can lead to exclusion of varying amounts of intrinsic raw material waste created during earlier stages of production.

We must also consider that current measures of process greenness do not explicitly account for complexity of the target molecule and availability of technology to make it.

This is important – APIs are not all created equal, and their manufacturing process complexities vary greatly.

Lastly, pharmaceutical firms have little incentive to develop 'optimally green' manufacturing processes due to high project attrition rates during development, limited patent lives of medicines, and perceived regulatory risks associated with the filing of greener and more economical second-generation processes.

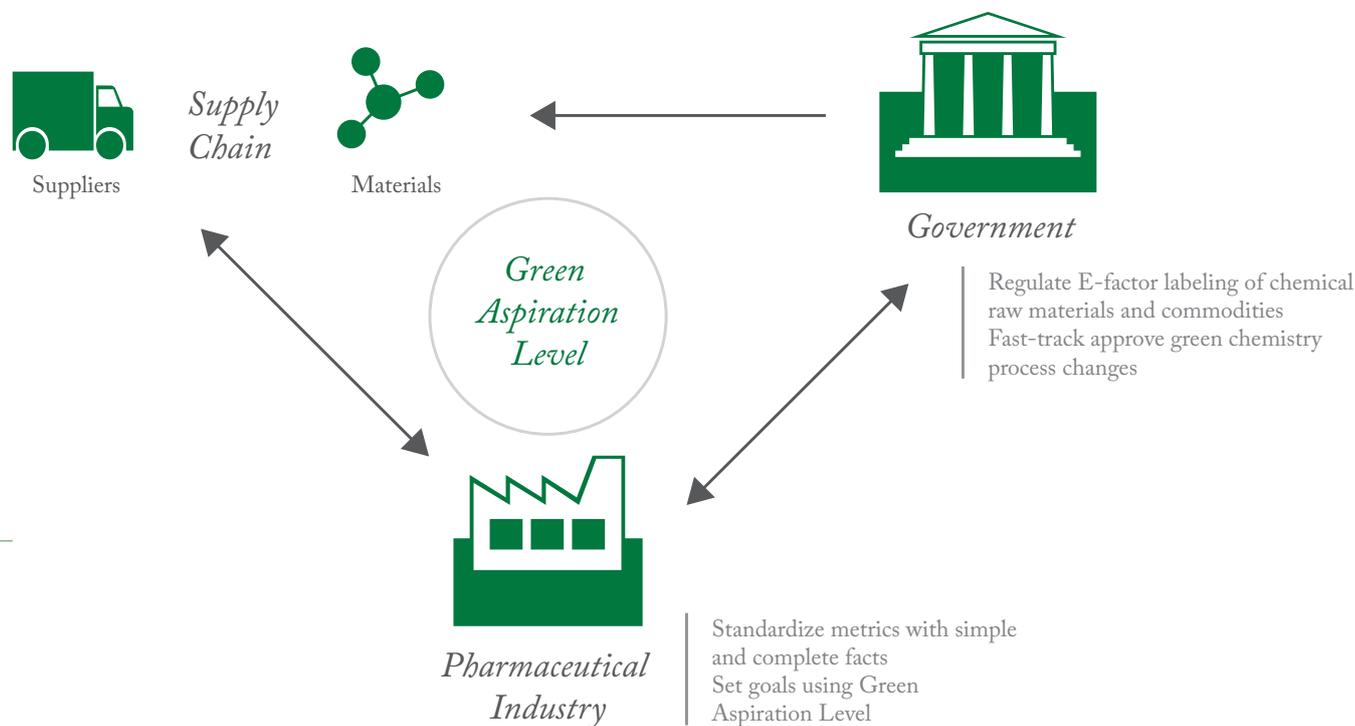
In an attempt to tackle some of the barriers to green chemistry, we recently created the Green Aspiration Level (GAL) concept as a metric to quantify the environmental impact of producing a specific pharmaceutical agent, while

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taking into account the molecular complexity of the API (5). GAL also clearly defines process starting points, and utilizes the complete E-factor as the mathematically simplest concept to derive the amount of chemical waste generated from the entire manufacturing process. In addition, GAL utilizes process waste data generated by the American Chemical Society Green Chemistry Pharmaceutical Roundtable (ACS GCI PR) to define average industry process performance as a reference point of comparison (6). Though the science of measuring molecular complexity is still in its early stages, GAL also took advantage of Baran's simple yet effective process ideality methodology, which represents both molecular complexity and the degree of optimal implementation of available chemical technology (7).

The result? GAL allows, for the first time, the objective assessment of green process performance relative to industry peers, thus giving scientists and managers a much-needed tool for measurement. Since it is quantifiable, GAL will also allow

Figure reproduced from (5) by permission of The Royal Society of Chemistry.



governments to sponsor green pharmaceutical manufacturing initiatives by considering incentives such as fast-track regulatory approvals for green processes, and regulations such as labeling of commercially available raw materials with complete E-factors.

We believe GAL can play a critical role in breaking down the barriers to broad adoption of green chemistry in the pharmaceutical industry. A critical first step is to get buy-in from the industrial community, which may best be achieved through dialogue within collaborative pharmaceutical consortia, such as the International Consortium for Innovation & Quality in Pharmaceutical Development and the ACS GCI PR. With their help, we could implement the new measuring tool across the industry, facilitate communication with governments to foster green chemistry initiatives through regulations and incentives, and make green chemistry part of national conversations about public policy.

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G Alan Kurose is President and CEO at Coastal Medical, Providence, RI.

Roger A. Sheldon is Professor (Emeritus) of Biocatalysis & Organic Chemistry at Delft University of Technology, The Netherlands.

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Smarter Synthesis

By *Leena Otsomaa*

Green thinking sometimes seems a long way off for those of us in medicinal chemistry, whose primary aim is to find drug candidates by utilizing chemical optimization. It can be hard to gauge an appropriate effort-to-benefit ratio from an environmental point of view. But in fact, there is much that we can do to promote greener working practices in our labs, particularly in terms of waste.

To bring green thinking to our medicinal chemistry labs, in 2014 we carried out an assessment of our activities and held a series of workshops on improving sustainability. Annual in-house data on waste and solvents were collected; for example, from electronic laboratory notebooks. The solvents used were checked against the solvent guide developed by the CHEM21 consortium to assess their environmental impact. Data collected on waste were compared to the number of test compounds synthesized and the scale of repeated batches. We found we were producing roughly 12 kg of waste per gram of test compound, and that 10 percent of that waste contained halogen, which is particularly damaging to the environment.

Having identified where we could do better, several workshops were run for all our personnel. The goal was to stimulate discussion on how much waste we produce and get everyone committed to contributing to increased sustainability. Principles for categorizing solvents, reagents and reaction conditions according to environmental impact were presented in the workshops. Then smaller sub-teams looked at how to apply green thinking in our daily work and a dedicated action group was formed to ensure execution of practicable suggestions and keep us on-track with our long-term sustainability commitment. To widen the impact of the measures, we also shared these with all our contract research organizations (CROs) in regular face-to-face meetings.

In general, many of our efforts targeted the planning phase of the optimization cycle in discovery. Good planning is critical if you want to achieve better compounds and synthesis routes. In the past, a medicinal chemist's productivity was measured by the number of compounds generated; however, future measures will focus on efficiency in structure design.

The focus will be on how many compounds were synthesized before the next level of target profile could be reached (hit, lead, pre-candidate) and how long it took. Quality rather than quantity in structure design reduces waste!

We have also agreed to update our internal process for smooth and efficient initial early scaling up from milligrams to grams or tens of grams based on green thinking. The revised process description will provide guidance for scientists on what is important to consider at each scale, or each repeated batch. Practical suggestions included avoiding unnecessary purifications, higher concentration of the reaction conditions, greener solvents and reagents, bringing back 'old fashioned' crystallization in purification, filtering literature searches by greener reagents, and many more.

**"WE ARE CONFIDENT
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THE ENVIRONMENT BUT
ALSO ACCELERATE THE
DISCOVERY PROCESS."**

Many good suggestions from the workshops have been implemented and people across the department have been motivated to bring green thinking into their daily work. It's not just scientists, either – in fact, technical staff were some of the most interested in green chemistry. CROs were also interested to hear about our efforts, although it remains to be seen how far they will adopt green thinking into their activities and how we can monitor that development. Interaction with our local academic institutions will be important if we are to stay at the forefront of green chemistry. In the meantime, we will continue to measure waste produced and efficiency of structure design on an annual basis, with a view to setting specific targets once we have a clearer understanding of the trends.

Most encouragingly from what we have seen so far, we are confident that green thinking can not only help the environment but also accelerate the discovery process.

Leena Otsomaa is Head of Medicinal Chemistry at Orion, Espoo, Finland.

Greening Biopharma



At Genentech, a member of the Roche Group, the Green BioPharma program aims to bring sustainability into R&D labs. Green BioPharma is an extension of the group-wide Green Chemistry program and focuses on the design, development and implementation of biological and chemical products and processes that reduce or eliminate the use and generation of substances hazardous to human health and the environment. We spoke to Green BioPharma Program Manager Kristi Budzinski to find out more.

What was the main catalyst for the scheme?

The catalyst was really employee interest. Our employees are very engaged in sustainability and wanted to merge that with the scientific work they do. We hosted a 'lunch and learn' session on Green Chemistry, which further piqued employee interest in having a scientific approach to greening R&D. As Genentech became more integrated with Roche, we became more active in their technical working group on Green Chemistry and wanted to develop a similar program for large molecules, giving rise to Green BioPharma.

How environmentally unfriendly are labs?

Laboratories have unique environmental challenges. Biology experiments have stringent sterility needs, which are met through higher air change rates than your typical office environment and the use of single-use supplies, mostly made of plastics. These plastic supplies are typically not labeled for recycling and may be perceived as unrecyclable by local municipalities. Additionally, numerous pieces of small electronic equipment are used to analyze samples and collect data, and until recently this equipment was not necessarily designed for energy efficiency, resulting in a large plug load. Biological samples, in particular, must be stored at low temperatures (-80 °C) for long-term preservation. These freezers use enormous amount of energy, often as much energy as two or three households every year. Recently, we have begun switching out older, inefficient freezers with new

Stirling freezers, which use half as much energy and can be cooled using non-halogenated refrigerants.

How do individual Genentech labs get involved?

Individual lab assessments provide a specific environmental footprint summary in terms of energy use, cold storage use, waste generation, and supplies. We provide lab managers with a list of recommendations for greening their lab based on this data. Some examples include using programmable timers to turn equipment off overnight and on weekends, increasing awareness of lab recycling (for example, by adding appropriate collection containers), and recommending green supplies (non-hazardous alternatives, less packaging, more efficient assays, and so on). Labs that complete 50 percent of the recommendations receive a "Green Lab" flag that designates them as a peer resource for other labs to learn about greening up their space.

Why has the program been such a success?

The tremendous support from both employees and management have really made the program a success. We have a cross-functional steering committee with representatives from major functions within Genentech who help set long-term goals, provide project support, and raise awareness within their functions. Environment, Health, and Safety adopted Green BioPharma as a beyond-compliance program and provided full-time program management support, which allows for more thorough data collection, metrics building, and project follow through.

How would you advise other companies who want to set up a similar scheme?

Establish both top down and bottom up support. Make sure that the program manager has laboratory experience so that he or she can speak the same language as the scientists. Most importantly, use data to drive projects and gain support – scientists love data!

Sustainable Ingredients

By *Daniele Piergentili*

Climate change, health challenges, and resource inefficiencies or shortages are very high on the agenda of societies around the world. And rightly so – after all, by 2050 nine billion people will share Earth; nine billion who need food, water, energy, housing and medical attention. It is one of the most important tasks of our time to produce high-quality and safe products while saving resources and ensuring quality of life for both today's and tomorrow's generation.

Sustainable Solution Steering provides us with a 360-degree view on the sustainability performance of our 50,000-strong portfolio across all industries; it is an essential step in committing and contributing to value chain-specific needs from various industries. BASF has a long history of implementing sustainability initiatives in its organization, but Sustainable Solution Steering goes one step further. It creates the necessary transparency to successfully implement sustainability standards into business activities. After all, if we don't have a full picture of the sustainability impacts of each product, how can we seek to improve the portfolio as a whole and promote solutions with clear sustainability benefits?

The meaning and focus of sustainability varies from industry to industry, so Sustainable Solutions Steering begins with market needs and industry definition of sustainability and takes industry standards into consideration. For our pharmaceutical industry customers, regulatory aspects and GMP quality standards are important factors. Based on such standards, we then assess each of our products against current and future industry requirements and assign them to one of four categories:

- Accelerator: substantial sustainability contribution.
- Performer: meets basic sustainability standards.
- Transitioner: has a specific sustainability issue, which is being addressed.
- Challenged: significant sustainability concern identified; action plan in development.



Having started the first pilot workshop in 2011, we have now assessed the company's entire portfolio involving R&D, product safety, marketing and sales teams. The outcome of the analysis is that many of our Pharma Ingredients & Services products already lie in the Accelerator category and none of them are in the Transitioner or Challenged categories. A good example of an Accelerator product is Kollicoat IR, which is primarily used as a coating excipient for immediate release of drugs from tablets or other solid dosage forms, and allows mixing without the addition of plasticizer. Furthermore, higher coating concentration and higher spray rates significantly reduce the coating time and reduce energy and water consumption in the coating process. Another good example of our continued effort in increasing our number of Accelerator solutions over time is our omega-3 fatty acids portfolio. We have implemented a stringent program to assure that our raw materials come from evaluated sources of healthy fish stocks.

"SUSTAINABLE SOLUTION STEERING PROVIDES US WITH A 360-DEGREE VIEW ON THE SUSTAINABILITY PERFORMANCE OF OUR 50,000-STRONG PORTFOLIO ACROSS ALL INDUSTRIES."

Putting in place our Sustainable Solution Steering approach has been a real journey for us and has helped to harmonize methodologies and understanding of sustainability within the organization. The next major step is to work even more closely with our external partners (customers and suppliers) in order to extract maximum value from our joint effort in the area of sustainability. Sustainability is a journey we can only successfully complete if we work together!

Daniele Piergentili is Vice President, Global Marketing, BASF Health and Nutrition, Florham Park, NJ, USA.

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A Fresh Pair of Eyes



Global healthcare company GlaxoSmithKline (GSK) has pledged to be carbon neutral by 2050. As one of the steps towards this goal, GSK's Engineering Centre of Excellence has developed and led Energy Reduction Events across all of its global sites. But why stop at sites within the company? GSK has now started to help suppliers identify opportunities to reduce energy use and embed changes in their sites geared towards a more sustainable future, using similar events at their own sites.

"At our own sites, we were typically finding anywhere between 20 and 30 percent energy reduction opportunities," says Sophie McSweeney, Utilities Commodity Buyer at GSK. "At each site, we considered the different processes and operations, and then how we could reduce energy requirements; for example, by reducing the amount of times you need to turn the machines on." In particular, GSK found a lot of potential savings associated with heating, ventilation, air conditioning (HVAC), compressors and lighting. "We also looked at whether we could implement renewable energies, such as solar, wind or biomass, at sites. The whole process was about making operations as efficient as they could be and then looking at replacing the source, otherwise you are specing something to a site that's not optimally efficient."

GSK offers a range of different Energy Reduction Events; the most comprehensive lasts for four and a half days. There is also an advance data gathering exercise to map existing energy processes.

- Day 1 - Designing. Assessing the data and what initial opportunities there might be for energy reduction.
- Day 2 - Measuring. Touring the site and seeing processes in action.
- Day 3 - Assessing and identifying opportunities. Narrowing down the actionable energy-reduction opportunities.
- Day 4 - Quantification and tracking. Developing a list of projects.
- Day 5 - Feedback. Developing a brief and feeding back to senior stakeholders.

"It's not an audit and it's not GSK engineers telling suppliers what they should be doing," says McSweeney. "We encourage collaborative working so that the site staff can utilize the expertise we bring and develop their own projects that suit their business. On the final day, it is not GSK who present the findings to senior stakeholders, but the internal engineers and operational personnel."

"WE ENCOURAGE COLLABORATIVE WORKING SO THAT THE SITE STAFF CAN UTILIZE THE EXPERTISE WE BRING AND DEVELOP THEIR OWN PROJECTS THAT SUIT THEIR BUSINESS."

Suppliers can sometimes be sceptical at first. Will the audit actually deliver any real savings or benefits? Will the time and effort involved suck up valuable human resources? Typically, once the Kaizen events begin and the teams involved are presented with some eye-opening facts about inefficiencies, attitudes to the whole process quickly change. After all, finding out that half of your company's energy bill is taken up by HVAC usage can be quite a shock. In this case, the Kaizen might help by suggesting opportunities to optimize building management systems. And discovering that your old chillers and freezers are far from efficient also prompts change – especially when capital investment on newer equipment can be recouped through reduced energy costs. The solid combination of environmental benefits and cost savings suggested by Kaizen sessions is usually sufficient to attract corporate interest – which helps drive the potential benefits highlighted by Kaizen sessions into practical steps much faster.

"A fresh pair of eyes," says McSweeney, is the main benefit to suppliers. "Someone external can challenge why something has to be the way it is and then both sides can work collaboratively to come up with the solutions. In the end, this will drive value for both GSK and its suppliers."

Webinars



Virtual
Events

The Sweet Revolution in Glycan and Antibody Separations

Monoclonal antibodies and other similar biotherapeutics are playing an ever more important role in the treatment of autoimmune diseases and cancers. It is predicted that within a few years, seven of the top ten pharmaceuticals will be antibodies.

Unfortunately, these proteins are extremely hard to characterize, due to an almost infinite number of variants, exacerbated by post translational modifications such as charge variance and aggregation. The number, type and location of glycans adds a further degree of complexity.

We discuss these difficulties and also the current technologies used to maximize separation capabilities and structural elucidation.

Webinar date: 31st March (8am Pacific, 4pm GMT, 5pm CET)

Register Free at: <http://tmm.txp.to/sweet-thermo-March/web-reg>



The Sweet Revolution in Mass Spectral Characterization of Glycosylated Antibodies

Protein-based therapeutics represent an increasingly significant part of the biopharmaceutical market. In order to fully characterize these novel materials, they must be analysed in both their intact form and also when fragmented into sub-units such as peptides.

Unfortunately, these proteins are typically highly heterogeneous, with many possible charge states and structural variations as well as post-translational modifications such as glycosylation or addition of other small functional groups.

Regulatory bodies such as the FDA and EMA require that these biotherapeutics are thoroughly characterized. As a result, extremely high resolution accurate mass spectrometry is required for a complete understanding of the protein structure.

Webinar date: 14th April (8am Pacific, 4pm GMT, 5pm CET)

Register Free at: <http://tmm.txp.to/sweet-thermo-April/web-reg>



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¹The Next Frontier: Indonesia - 2013 IMS Health Incorporated and its affiliates.

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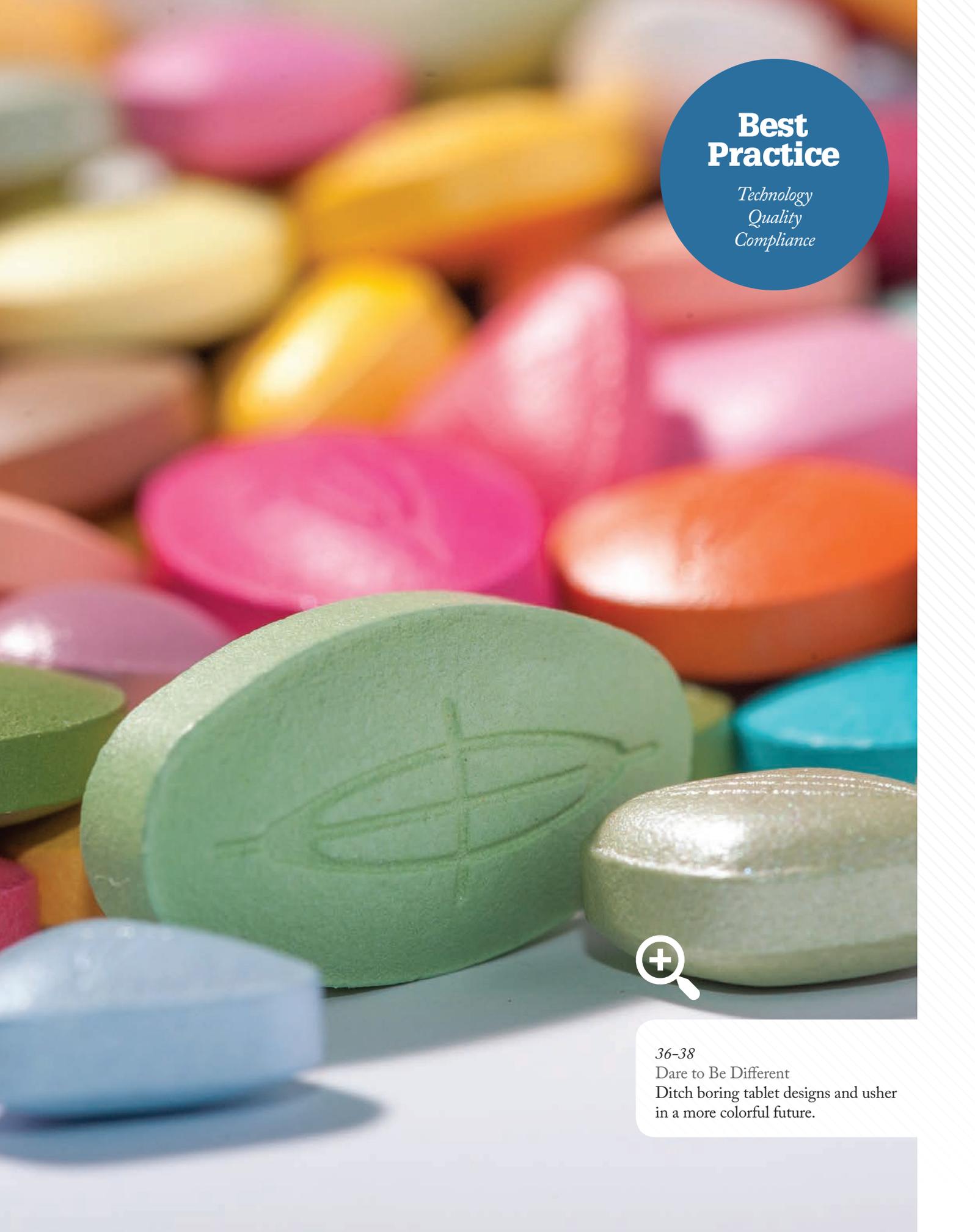
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Dare to Be Different
Ditch boring tablet designs and usher
in a more colorful future.

Dare to Be Different

With regulators looking for more differentiation between tablets, we must be bolder with solid dosage designs. There's a whole world of color and shape out there – let's give our vanilla world a makeover.

By Charlotte Miller

“You’re a tablet design specialist – what does that entail?” people often ask me, assuming that the job of designing tablets is rather simple. But so many different shape, size and color options are available. The design process starts with a whole host of questions – the biggest: what is suitable for the target patients? Tiny tablets might be perceived as the easiest to swallow but they are hard to handle and easy to drop. And what about color? The one you’ve chosen for your tablet may not be suitable for the Japanese market (although it’s perfect for North America). And the manufacturing department may like that simple tablet design, but is it too easy to copy? Things are already getting complicated...

Unique designs are important. They can help to make medicines memorable to patients, caregivers and pharmacists, and may also make a tablet easier to take. From an anti-counterfeiting point of view, unique design could also make products more difficult to copy. There are also production benefits; a unique design gives you differentiation on the packaging line, making it easier to visually spot a mix up and prevent product recalls before they ever happen.

The advantages of better design have been acknowledged by the FDA, which issued draft guidance in 2013 – Safety Considerations for Product Design

to Minimize Medication Errors (1) and New Guidance for Industry: Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules, in 2014 (2). In essence, too many products and dosages look the same and there’s a risk that dispensers may distribute the wrong product, or that people taking more than one medicine (increasingly common in our aging population) will get their pills mixed up. Regulators now expect companies to consider aspects such as size, shape, color and differentiation between dosage strengths prior to marketing. It’s a brilliant initiative that’s made the industry wake up to the importance of tablet design. Similar-looking dosages, especially plain white tablets, may not get through the regulatory process. Your tablet needs to be different.

So where do you start? When I’m creating a new design, there are several key questions that I ask clients to help me deliver the most appropriate design. How big is the tablet? Who will be taking it – everybody, the elderly, only females or males? What is the therapeutic area? I also encourage the client to involve all stakeholders in the design discussions. A common mistake is to assume that you only need the R&D department involved in tablet design meetings, since they are the ones developing and formulating the drug, but if you include regulatory, manufacturing and marketing you can avoid a lot of problems down the line – everyone needs to know that there are limits! Regulatory will understand why they can’t have a bright yellow tablet, and manufacturing can voice their concerns on tablet shape, and offer guidance on what will and won’t fit with production lines.

I also conduct research on other medicines and co-medications in the same therapeutic area, so that I can identify opportunities for differentiation. Broadly speaking, the main design elements to consider are size, shape and color.

Tiny troubles

When is a small tablet preferable to a larger tablet or vice versa? The ideal size of a tablet varies depending on the intended patient group, but the actual size is often set depending on the formulation and dosage. If your dosage is 1300 mg then a tiny tablet is impossible, and this is where shape is extremely important. By altering the shape it’s possible to give the perception of a smaller, more streamlined tablet. If you have a very big tablet, it could also be worth considering more drastic changes; I’ve spoken with consumers before who say they would rather take two smaller tablets than one large one.

Is smaller always better? A study looking at pediatric populations found that tiny 5 mm tablets were not as attractive to children as expected, with interviewees being concerned about losing the tablet and some worried about swallowing it (3). The slightly larger 10 mm tablets were preferred.

Older patients also tend to prefer larger tablets because they are easier to handle (4). Again, you can use shape to change a patient’s interaction with the tablet. For example, by changing the dimensions you can lift it slightly higher off the surface, which makes it easier to pick up. Ideally, you need a good balance between ease of swallowing and ease of handling. Figure 1 shows how different shapes can affect the perception of size.

The shape of things to come

For some companies, exploring different shapes can be daunting because it can affect the dissolution profile. Most companies do their R&D work on a standard round or oval tablet and it’s not until around Phase III that they start to think about the final product appearance. Obviously, the earlier you think about your tablet design the better, but it’s certainly not too late at this point to change the shape. In an interesting study from 2009, we demonstrated the importance of



Figure 1. Tablet shape can affect the perceived size, and improve distinction and memorability.

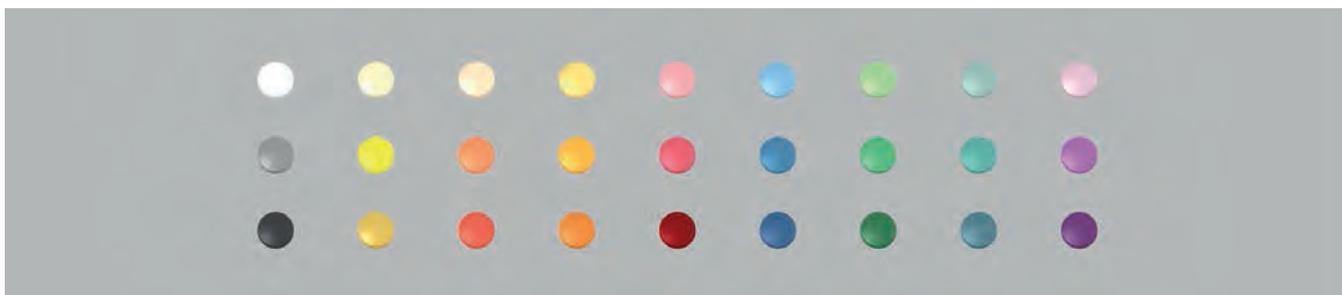


Figure 2. Just some of the many colors available.

surface area-to-volume ratio on drug release from hypromellose matrices (5). I can use software to manipulate the mass properties of a tablet and change the shape without altering the dissolution profile. The software also allows me to preview other design options such as color and logo placement, which really helps speed up the process.

When I'm working with clients, I look at their needs and their product before presenting them with different shape and color options. Often, companies include these in their regulatory submission to show that they have considered the design of their tablets. It's not just a case of picking a shape at random. Once again, the shape must match the needs of patients. For example, a heart-shaped tablet may be appropriate for heart medication, but it depends on the tablet size. A heart-shaped tablet of 700 mg, for example, may be perceived to be too big to swallow. Any bigger than this and more elongated shapes are more popular.

Suitable shapes will also vary depending on how robust the core formulation is. Due to the nature of their ingredients, nutritional supplements tend to be less robust, which means that some shape options aren't possible. Companies' manufacturing lines and tablet tooling also

vary, which may limit options. You need to consider the final choice carefully.

“When it comes to making a memorable tablet, color is without a doubt the most important aspect.”

Expand your palette

I've spoken to people who say that they don't care what color their medication is so long as it's effective. After all, color is a sensation that only exists in the brain and will not physically affect ease of swallowing in the same way as tablet size and finish. However, studies have shown that people do in fact prefer certain colors of pills, however unconsciously. We need people to take their medicines, so helping to encourage compliance is worthwhile. Color has other benefits too; I talked briefly about memorable shapes above but, when it comes to making a memorable tablet, color is without doubt the most

important aspect. Color also improves brand recognition – just think of Viagra with its iconic blue color (and memorable diamond shape).

How we feel about the tablets we are taking can also be influenced by color. In 2005, Colorcon conducted a study where 2,000 patients were asked to align different emotional attributes with different colors and shades (6). White aligns with 'safe', which isn't surprising given that historically many tablets are white. But yellow and pink are also good choices and will aid product differentiation. However, attitudes towards color are market-dependent. For example, red can be seen as powerful or dangerous depending on the country. Results will also vary with gender and age demographics. As well as taking into account emotions, you can also use color to indicate what time of day a tablet should be taken. Some people associate dark tablets with being taken at night and lighter tablets being taken in the day. A good example of this is day/night cold remedies, where yellow for day and blue for night are used. At the moment, people are not used to seeing bold-colored tablets, but I think this will change as companies make more effort to differentiate products. Figure 2 shows just a few of the many colors and shades that are available.



Five Top Tips for Tablet Design

1. Carefully consider the design of your tablet and how to differentiate multiple dosage strengths. Regulators may reject a submission where tablets are not well differentiated.
2. Make it easier to swallow by paying close attention to physical attributes such as shape, size and coating.
3. How a tablet looks can affect how patients feel about their medicine and influence compliance. Choosing the right color may prevent medication errors.
4. Consider the right tablet shape, size and colour for your patient population to improve patient adherence.
5. The more unique and complex the tablet design, the more difficult it is for counterfeiters to make convincing copies.

When thinking about color, your choice will be strongly influenced by ingredients and what the regulators in various parts of the world have to say. Some countries have restrictions on different pigments, so you may have to consider country-by-country formulations. At Colorcon, our regulatory department helps ensure the choice of suitable pigments and we use a color decision tool to show what customers can use around the world and breakdown by region: Europe, North America and Japan. For Japan, the color options are typically much more limited

because of regulations on dyes; for example, you can't use brightly colored aluminum lake pigments in Japan. Iron oxide-based colors are truly global and offer many shades, but are from a more reserved palette of beiges, yellows, browns, and grays.

As well as color, you can also add markings, or even images, to your tablet using edible inks, which really helps to set products apart. If counterfeiting is a big concern, there are technologies now available that can "fingerprint" the product through incorporation in the tablet coating.

The final finish

I've discussed some of the basic elements of tablet design and hopefully inspired you to think more creatively about your tablets. But size, shape and color are not the whole story. Whether a tablet is matte or glossy also influences patients' thoughts. Which would you prefer to take? A high-gloss tablet is visually appealing and has been shown to be easier to swallow (7). Most companies choose to apply a film coating to get that glossy effect. A film coating can also be used to mask unpleasant tastes and odors, improve mechanical integrity and protect the tablet from moisture. Covert chemical markers can also be incorporated into a film coating to help prevent counterfeiting, as well as specialized flavors and aromas that are identifiable by patients.

With so many options available, there's a trend away from producing a plain white tablet. We're already starting to see companies being bolder with their designs and I believe patients will find these alternative colors and unique shapes appealing and memorable. The great news for pharma companies is that being different needn't result in manufacturing challenges or increased costs. So don't be afraid to stand out. You can make life easier for patients – and much harder for counterfeiters. Dare to be different and reap the rewards.

"We're already starting to see companies being bolder with their designs and I believe patients will find these alternative colors and unique shapes appealing."

Charlotte Miller is a Tablet Design Technologist, BEST – Unique Tablet Design Service – at Colorcon, Dartford, UK.

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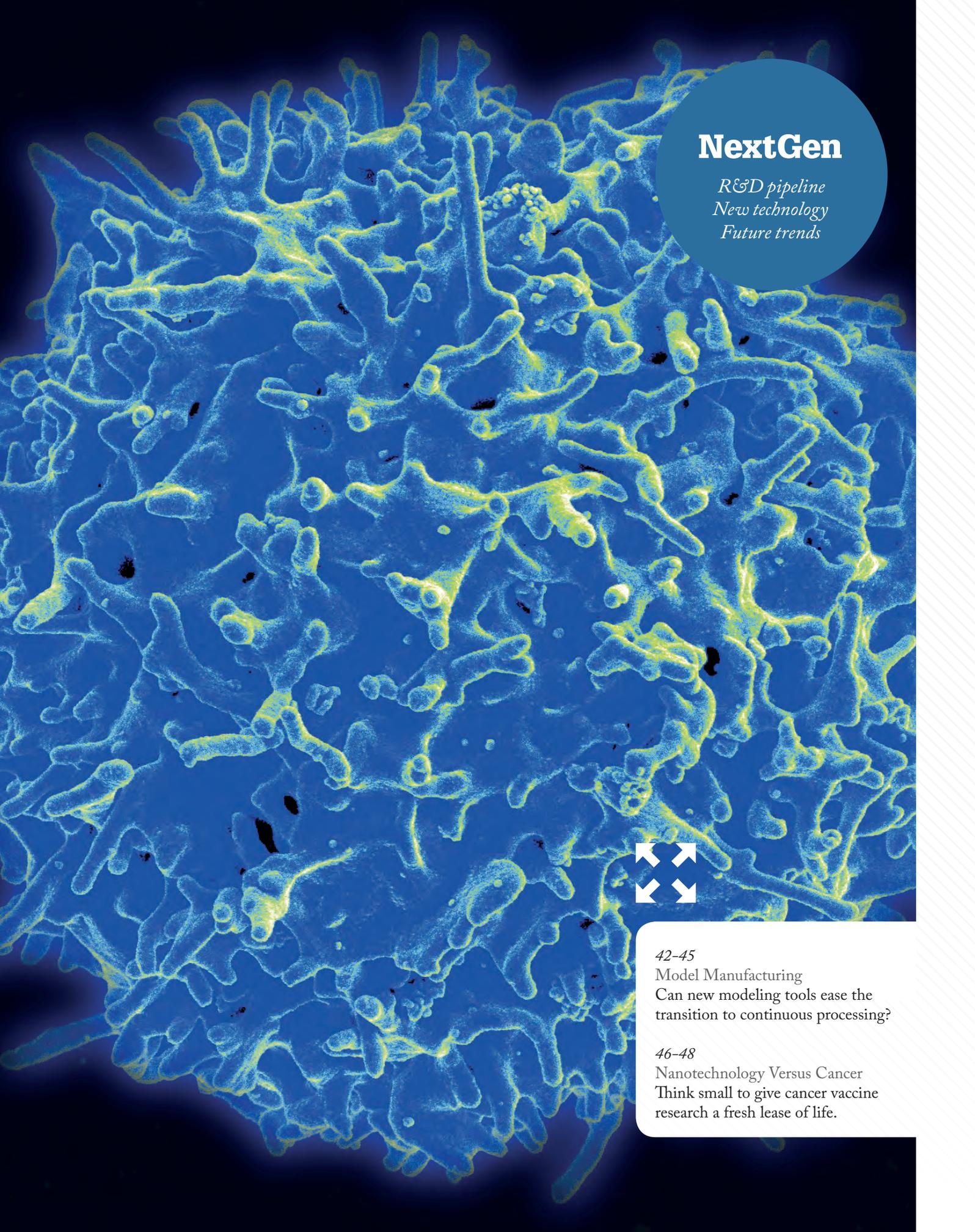


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Model Manufacturing

Can new modeling tools ease the transition to continuous processing?

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Nanotechnology Versus Cancer

Think small to give cancer vaccine research a fresh lease of life.

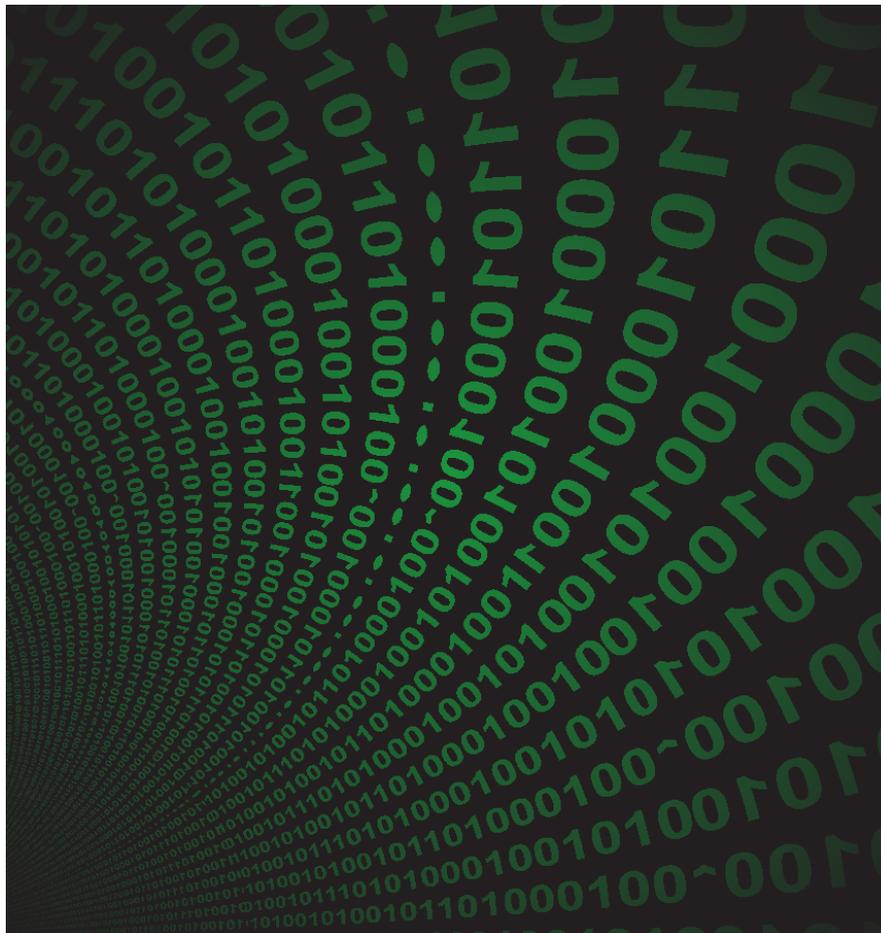
Model Manufacturing

Our 'dynamic flowsheet model' links API purification and processing with downstream tablet manufacturing to provide better control of the process variables and, ultimately, the critical quality attributes of the final pharmaceutical product. Here's how.

By Maitraye Sen, Ravendra Singh and Robit Ramachandran

The advantages of continuous processing schemes have been discussed by many in the industry (1-3), but the US FDA's stringent regulatory guidelines have somewhat hindered implementation. Despite this, progress is being made and the pharma industry is slowly moving from batch to continuous processing. As a result, it is necessary to have a clear understanding of the process dynamics and to develop suitable tools to help with the process design analysis. We believe that modeling and simulation can aid the transition.

A well developed, tuned, calibrated and validated model can be an effective tool in order to study the process dynamics or perform design, optimization and control studies. For instance, mathematical models can be developed that capture the dynamics of active pharmaceutical ingredient (API) powder processing operations, allowing for virtual experimentation and validation of new methodologies prior to implementation in the real plant. Design or optimization based studies require multiple trials; using a model instead of conducting several experiments will help to save resources.



In this article, we describe the development of our dynamic flowsheet model, which connects API purification and processing with downstream tablet manufacturing. The starting point for our work was the observation that the physical properties of API crystals have a wide-ranging influence on the critical quality attributes of the final dosage form. So, if we can establish a connection between API purification, processing and tablet manufacturing steps then it should be easy to control the process variables and obtain a final dosage form with the right critical quality attributes. The powder flow phenomenon is difficult to predict because of its inherent variability, so real-time feedback control and monitoring techniques are also

important, and emphasized in the FDA's process analytical technology (PAT) framework (4, 5).

Our model, the first of its kind, incorporates a multi-scale framework that stores information from different levels or scales. For example, in the case of powder flow, the particles are considered as discrete entities that can interact with each other and with the equipment boundaries in different ways. A discrete element modeling technique can simulate the flow pattern of each and every particle, and provide particle-level information that will be used in the process model to obtain important process variables. The advantage of using a multi-scale framework is that it helps to capture process dynamics more efficiently. In addition, we've developed

a robust control strategy for the process. This model will help to clarify the effect of upstream process parameters on the critical quality attributes of the downstream product.

Essential integration

The integrated process model links crystallization, filtration, drying and mixing in a continuous manner. Figure 1 presents the schematic of the flowsheet including the control loops, which we will discuss in the next section. We developed process models of these unit operations from first principles and then established a continuous connection between them.

The crystallization model is that of a cooling crystallization – as the temperature falls, the solute precipitates out in the form of nuclei, which grow to form crystals of different sizes. As the crystals are formed, the liquid solvent forms a thin layer on the crystal surface and often gets lodged within the crystal pores. The crystal size distribution (CSD) is a function of the nucleation and growth rate kinetics, which in turn are controlled by the cooling profile (the pattern in which the temperature is reduced over time), so changing this profile also changes the CSD.

CSD can have a considerable impact on mixing efficiency, so we used the CSD obtained from the crystallization process as an input in a discrete element method, which predicts the behavior of large numbers of small particles, for the continuous mixing model. The discrete element method simulations give the average particle velocity at specific locations inside the mixer as an output, which is then fed into the mixing process model. Our crystallization and mixing process models were both developed on the basis of a population-balance model methodology. Figure 2 shows the schematic of the multi-scale framework.

The output of the crystallizer, a slurry of API crystals in the mother liquor,

is connected to the input of the filter and the crystals are removed from the solvent. The crystals form a solid cake on the filter medium and, when dislodged, enter the dryer. The stream of crystals entering the dryer are of a particular size and contain considerable liquid content, as determined during the crystallization step. Although there is some size change associated with the drying process, it is quite minimal, so we can ignore it for the purposes of our model.

“A well developed, tuned, calibrated and validated model can be an effective tool.”

Once the API crystals are separated, purified and dried, they are sent to the mixer where they are mixed with an excipient to obtain the final pharmaceutical blend. The output variables from the mixing model are the variability of the product, expressed as relative standard deviation, and API composition of the blend. You can read more about the mathematical equations and multi-scale flowsheet model in our previous articles (6, 7).

Process control

We also developed a hybrid model predictive control (MPC) – proportional-integral-derivative (PID) control scheme for our flowsheet model (8). Control loops were developed for each of the unit operations, but we used a constant pressure gradient for the filtration process (by assuming an

ideal controller that can achieve the desired set point perfectly). In practice, the pressure gradient can be maintained by adjusting the flow of air or exhaust across the filter medium (9, 10).

The cooling temperature schedule is the critical process variable in crystallization and here we used a cascade control scheme (consisting of a slave and master controller). The master controller generates the set point of the temperature cooling schedule for the slave controller, and the temperature schedule is then achieved by varying the temperature of the cooling water that passes through the cooling jacket. We demonstrated the cascade loop with the aid of a hybrid MPC-PID design, where MPC is the supervisory controller, used to control the saturation concentration, and PID is the secondary controller, used to control the operating temperature. The saturation concentration of the solute is measured and fed to the MPC block, which generates the set point for the operating temperature controlled by the PID. In many instances, a cascade control loop has better performance than a single-loop control; for example, when there are long dead times; or when a disturbance affects an intermediate variable, causing a knock-on effect on the main control variable (11, 12).

For drying, the temperature of the drying medium, which in our case is air, is the critical control variable. Air at atmospheric temperature can be heated to the desired temperature by using superheated steam in a heat exchanger prior to it being sent into the dryer. For the mixer, there are two control variables of interest: fractional API composition of the final pharmaceutical blend and holdup. Mixer holdup is an important control variable as it can have a considerable effect on the product's variability. We controlled holdup by manipulating the weir length, having previously determined the effect of the

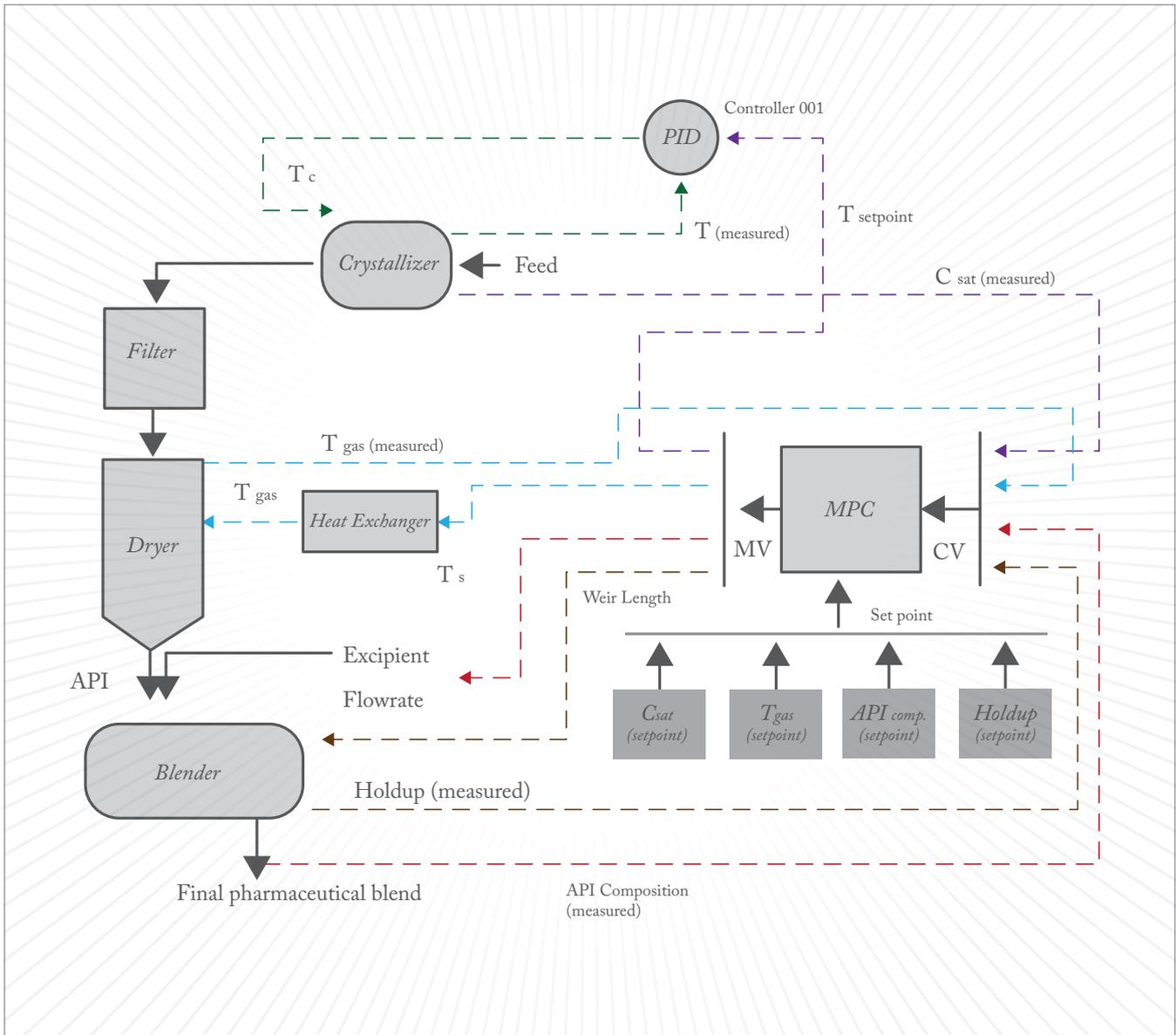


Figure 1. Closed-loop integrated flowsheet model. API: active pharmaceutical ingredient; MPC: model predictive control

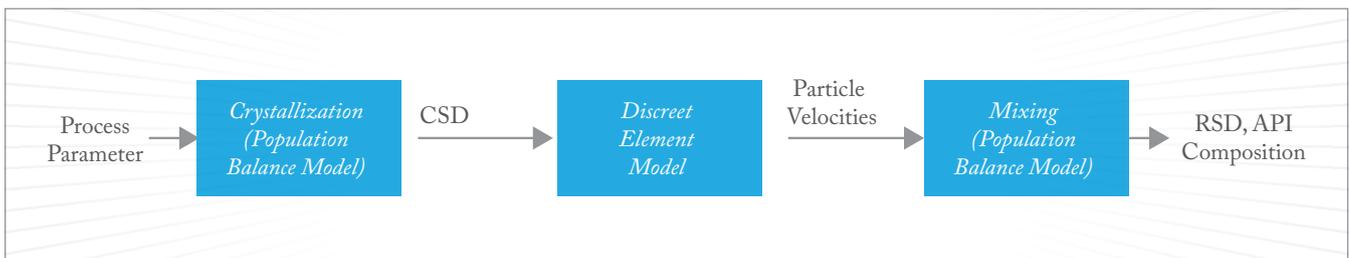


Figure 2. Multi-scale framework. API: active pharmaceutical ingredient; CSD: crystal size distribution; RSD: relative standard distribution; MPC: model predictive control; PID: proportional-integral-derivative.

“This integrated continuous flowsheet model, developed from first principles, connects the API purification and processing steps with a downstream tablet manufacturing operation.”

weir length on the holdup by running discrete element method simulations of the mixing operation.

As mentioned earlier, the control scheme is a hybrid - we used an MPC-PID hybrid control loop for the cooling profile of crystallization operation and the drying gas temperature; while API composition and holdup have been controlled with the help of MPC only. If you're interested in the design strategy of the hybrid control system, you can find details in a previous article (7).

And the results?

We evaluated the control loop both in terms of set point tracking and disturbances rejection. Disturbances rejection refers to the ability of the system to bring a process variable back to a fixed value - a bit like cruise control in a car. Set point tracking is the ability to adjust a variable to a changing value - say, when the driver increases the cruising speed. A step change was applied to the set point to evaluate the set point tracking ability, and sinusoidal disturbances were introduced in the

input signal to study the disturbance rejection. Using these two tests, we compared the performance of the MPC-PID control scheme with that of a PID (regulatory controller)-only scheme, with positive results. MPC-PID scheme stabilizes faster and has a high decay ratio, which is always a good thing for a controller. Looking at disturbance rejection for crystallization, again the hybrid scheme performs better. The same pattern was seen when looking at set point tracking and disturbance rejection for the drying gas temperature. Similarly, the performance has been evaluated for the mixing operation; once again the MPC scheme is better than the PID scheme.

Next steps

This integrated continuous flowsheet model, developed from first principles, connects the API purification and processing steps with a downstream tablet manufacturing operation and can be used as an effective tool to study the impact of the upstream process parameters or API properties on the efficiency of the downstream operation. The next steps will be to extend this flowsheet further by adding other operations for downstream processing (e.g., granulation, roller compaction, tablet compaction and tablet dissolution) for a complete quantitative analysis of continuous purification and downstream processing of solid dosage forms.

Maitraye Sen, Ravendra Singh and Rohit Ramachandran are from the Department of Chemical and Biochemical Engineering, Rutgers, The State University of New Jersey, Piscataway, NJ, USA.

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Nanotechnology Versus Cancer

With only one approved drug and many failures, the cancer vaccine field has lost some of its shine. Could nanotechnology brighten its prospects?

By Ronak Savla

We need a new type of weapon in the war on cancer. Chemotherapy, the backbone of cancer treatment, often brings initial success but cancers are notorious for relapsing in ever more aggressive and resistant forms. Traditional chemotherapies do not discriminate. They attack all rapidly dividing cells and are plagued by a narrow therapeutic index, numerous side effects, and high likelihood of resistance (1). Newer, molecularly targeted agents sidestep many of these problems, but often require lifelong treatment. And because these agents are relatively new, their long-term efficacy and safety are yet to be determined, and it is likely that we will see resistance develop over time.

Harnessing the immune system to fight cancer has become the Holy Grail of oncology. The potential is obvious — by using the body's own defenses, we could in theory avoid the problems of current therapy and provide new options for cancers that would otherwise be untreatable. Indeed, the journal *Science* named “immunotherapy of cancer” as its 2013 breakthrough of the year (2). Immunotherapy comes in several forms: immune-modifying agents (antibodies and cytokines); immune cell therapy; therapeutic cancer vaccines; and immune checkpoint inhibitors. Of these, therapeutic cancer vaccines have generally been regarded as having the greatest potential but, despite the tremendous

promise and years of research, there is only one FDA-approved cancer vaccine (Dendreon's Provenge) and dozens of failures. However, research into all types of cancer immunotherapy has been given a new lease of life by the approval of several checkpoint inhibitors in the past five years, and research on cancer vaccines continues.

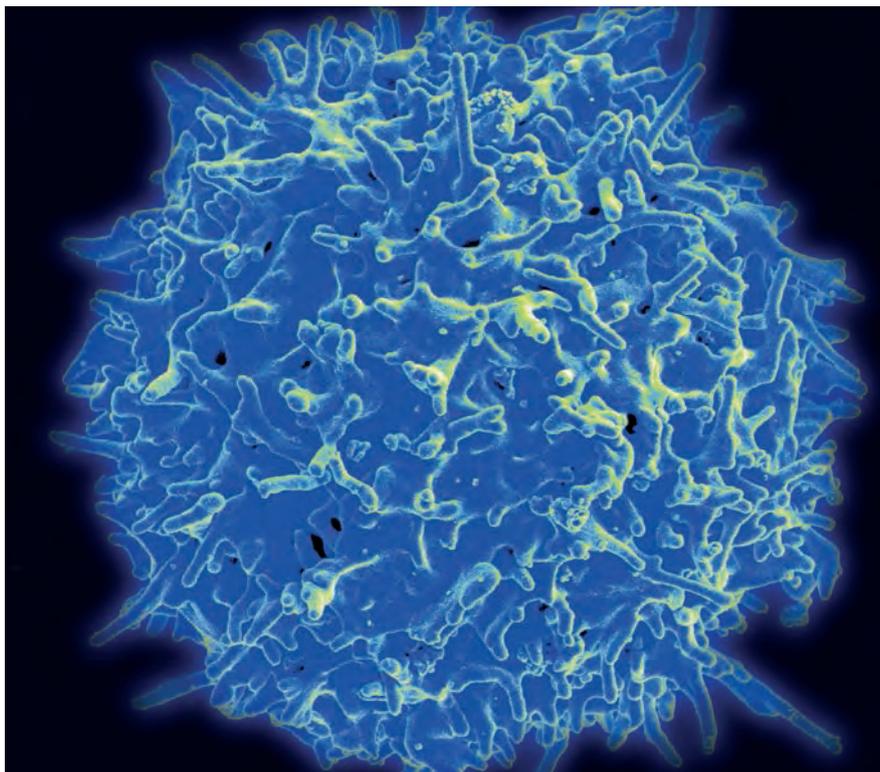
Cancer vaccines can be divided into four broad categories: peptide, tumor cell, dendritic cell, and DNA (3). Tumor and dendritic cell cancer vaccines can be further subdivided as homologous (derived from the patient) or heterologous (off-the-shelf). Although one might expect that homologous cancer vaccines would possess superior efficacy and safety, off-the-shelf products have the advantage of less labor-intensive preparation. Unfortunately, the discussion is largely academic, as none of these types of cancer vaccine have yielded the amazing improvements in survival that were hoped for.

Nanoparticles to the rescue?

Part of the problem is that the immune system has largely evolved to detect foreign antigens from bacteria, viruses and parasites. Cancer cells are not

foreign, but simply normal cells gone awry, which means that the immune system has difficulties recognizing tumor-associated antigens (TAAs), even when presented in the form of a vaccine. By delivering TAAs or DNA encoding TAAs directly to the cells of the immune system, nanoparticles can improve immune presentation and maximize the response. Nanoparticle formulations are already used for preventative vaccines such as Inflexal (liposomal influenza hemagglutinin), Engerix B, Gardasil, and Cervarix (4). Nanoparticles have another big advantage: they are customizable. The nanoparticle composition, surface functionalization, size, and loading strategy can all be fine-tuned to achieve the desired profile, with maximum efficacy and minimum side effects.

It is not enough to induce a strong immune response. For a cancer vaccine to be successful, it has to induce the right type of response. In broad terms, an immune response can occur either via a B cell antibody-mediated response or a cytotoxic T cell-mediated response (5). Immunogenic cancer cell death is primarily achieved by the latter, which therefore needs to be maximized. But to generate a



cytotoxic T cell response, antigens have to be processed and presented through major histocompatibility complex (MHC) Class I pathway. Unfortunately, most tumor antigens are presented by MHC Class II pathways. Nanotechnology can help – simply conjugating antigens with nano- and micro-particles can result in a thousand-times increase in antigen presentation via the MHC Class I pathway and can thus ensure a cytotoxic T lymphocyte response. Adding antibodies to the nanoparticle surface allows targeting of specific immune cells, ensuring that exactly the right immune response is activated.

Liposomes and polymer nanoparticles are the most commonly used nanotechnology approaches for cancer vaccines. These particles are frequently used so we have a great deal of experience working with and manipulating them, plus there should be few safety concerns when entering clinical trials.

Nanoparticle composition, size, shape, surface chemistry, and surface charge influence the magnitude and type of immune response. It appears that the size and surface modification have the greatest influence on antigenicity, adjuvanticity, inflammation, and uptake (6). However, there may be trade-offs between the various properties, which must be weighed when designing nanoparticle-based cancer vaccines.

Sizing up immune response

Nanoparticles used for vaccination strategies typically have a size range of 20-200 nm, which is smaller than many other antigens, such as emulsions, mineral salts, and whole cell vaccines. Many peptide antigens are small (<10 nm) and therefore dendritic cells and macrophages do not readily recognize them. The small size and high surface area to volume ratio of nanoparticles allows for a large loading capacity and can increase antigen exposure to dendritic cells. A nanoparticle size of

25-50 nm appears to yield the best results.

Nanoparticle cancer vaccines do not target tumors directly – they target dendritic cells. Dendritic cells, present in peripheral tissues and lymph nodes (7), are the primary antigen-presenting cells and help dictate whether an immune response will be induced and what type. The size of the nanoparticle influences the type of dendritic cells that antigens are presented to. When administered intradermally, larger nanoparticles (100 nm) interact with dermal dendritic cells. These cells must then migrate to the lymph nodes to generate a robust cytotoxic T cell immune response. Smaller nanoparticles (25 nm), however, can go straight to the lymph nodes. The lymph nodes are home to the majority of the body's dendritic cells, and are the only place where CD8+ dendritic cells are found, which activate cytotoxic T cell responses. The smaller size also translates to a higher uptake by dendritic cells and longer residence in the lymph nodes, resulting in a stronger T-cell based immune response.

So, in general, smaller is better. But there is such a thing as too small. Ultra-small nanoparticles (<10nm) have poorer receptor binding affinities and internalization than relatively larger nanoparticles, possibly due to dissociation of smaller nanoparticles prior to internalization. Ultimately, the size of nanoparticle chosen depends on the response you want to provoke. Immunization with nanoparticles of 40 and 49 nm diameter induced production of interferon- γ and a T cell-mediated response (8), the proposed mechanism of action for cancer vaccines. However, immunization with larger nanoparticles (93-123 nm) was ideal for inducing an antibody-mediated response. Shape also plays a part: spherical nanoparticles favor elicitation of a T cell-mediated response whereas rod-shaped nanoparticles lean towards an antibody-mediated response (Figure1).

Scratching the surface

The surface of the nanoparticle is the first thing that dendritic cells interact with. Therefore, it is unsurprising that proper surface modification is a key factor in whether a cancer vaccine will be successful. The first aim is to get the nanoparticle inside the dendritic cells. Positively charged particles tend to be more easily internalized than their negative counterparts, particularly for larger nanoparticles (9). This is primarily driven by electrostatic interactions with the negatively charged cell membrane. A positive charge is especially valuable for DNA vaccines as it will be more effective in condensing the DNA, protecting it from degradation, and traversing the cell membrane. The downside of positively charged nanoparticles is that there is more chance of interaction and uptake by other cells, leading to concerns over toxicity (10).

Another study found that dendritic cell maturation was accelerated when nanoparticles with hydroxyl surface groups were used, compared to those with methoxy surface groups (11). Many tumor antigens are soluble peptides that are weakly immunogenic by themselves; attachment onto a hydrophobic nanoparticle surface can improve their immunogenicity. Furthermore, the way an antigen is attached onto the surface influences the immune response magnitude. Conjugated antigens tend to result in higher T cell responses compared with antigens that are adsorbed onto the nanoparticle surface (12).

Targeting is another advantage of nanoparticles. Attachment of antibodies, peptides, and aptamers can help increase the interaction with and accumulation in a certain type of tissue or cell. Furthermore, the use of a targeting ligand leads to receptor-mediated cell uptake. Dendritic cells recognize antigens using C-type lectin receptors, including mannose receptors. Decorating nanoparticles with mannose has been shown to increase

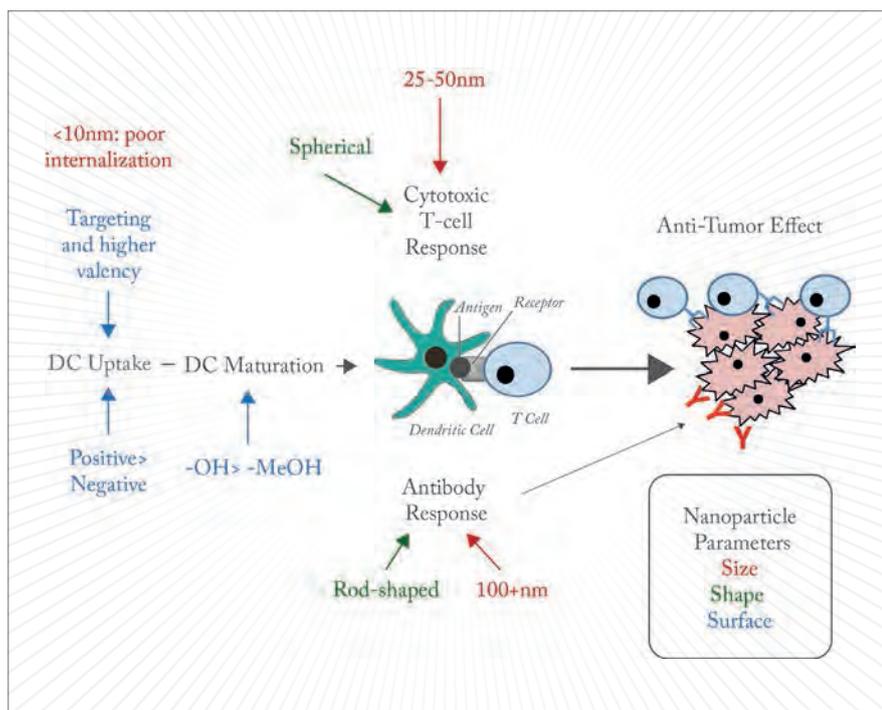


Figure 1. Altering response. DC: dendritic cell. Nanoparticle characteristics affect the performance at different aspects of dendritic cell-mediated immune activation and response.

interaction with dendritic cells and a higher valency of mannose ligands improves uptake (13).

Boosting response

Adjuvants – additives to boost immunogenicity – can make or break a successful vaccine. Nanoparticles themselves can act as adjuvants. Traditional adjuvants, such as mineral salts and emulsions, form a depot and slowly release antigens. Nanoparticles can produce a similar effect by encapsulating antigens within a liposome or polymer matrix. The delayed onset of action seen with nanoparticle formulations and co-delivery of antigens with adjuvants or immunostimulatory chemotherapeutics may result in higher immunogenic cancer cell death.

Cancer vaccines have so far mostly failed to achieve sufficient immune responses in terms of both intensity and duration. Even where vaccines have elicited an immune response, this has not translated to effective tumor killing. Nanotechnology is primed to accelerate the development of this straggling field. The flexibility of nanoparticle design could finally unlock directed immune responses with adequate magnitude.

There's an important caveat. So far, nanotechnology-based cancer vaccines have been limited to laboratory tests; the real test will be whether nanotechnology-based cancer vaccines result in improved patient outcomes and survival. Given the multifaceted, ever-evolving nature of cancer, and the disappointing results of previous 'cures', it may be best not to pin too much hope on a single approach. For the best chance of meaningful survival improvement for patients, we may need to look at a mainstay of cancer treatment – combination therapy. Combining cancer vaccines and checkpoint inhibitors could be an interesting potential therapeutic regimen, with cancer vaccines providing acceleration of the immune response and checkpoint inhibitors 'releasing the brakes' on immune system inhibition. When you are dealing with an enemy as deadly and evasive as cancer, a single solution is unlikely to be enough. That said, if nanoparticles can fulfil their promise, we will be adding a powerful new weapon to our armory.

Ronak Savla is an Applied Drug Delivery Fellow with Catalent Pharma Solutions through the Rutgers Pharmaceutical Industry Fellowship Program.

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Smooth Operator

Sitting Down With...

James Christie, Project Director for
Manufacturing, Association of the British
Pharmaceutical Industry (ABPI), London, UK.

What attracted you to your new role?

A large part of my role is shaping the newly created Medicines Manufacturing Industry Partnership (MMIP), which brings industry and government together to help boost medicines manufacturing in the UK. It's exciting to be at the very beginning of creating an entity that could be transformational for the sector. I want to look back in 15-20 years' time and see that we've helped to re-energize medicines manufacturing. And the MMIP – led by ABPI and the BioIndustry Association (BIA) – can really make a difference.

How did you get into pharma manufacturing?

In some ways, I got into the industry through the back door. I started my career at the bench as a research technician at the Chester Beatty Institute of Cancer Research in London. It was through a chance meeting with a gentleman from Wellcome – Mike Barton – that I started to understand what industry actually did in terms of research, development and manufacturing. He painted an excellent picture of the opportunities within big pharma and I was aware that there was a link between my Institute and Wellcome. Six months later I was offered a role at Wellcome's Beckenham site.

Although I enjoyed bench research, my father was an engineer and I came from an industrial area so that was always in my DNA. I wanted to get involved in something more practical and tangible.

How did things progress at Wellcome?

I spent 10 very informative years at Wellcome; it put me on the front line of innovative medicine. As a Process Biologist I was involved in the design, build and operation of industrial manufacturing facilities for monoclonal antibodies. It was an extremely creative period, and gave me the opportunity to work all over the world. My time at Wellcome culminated in the build and

launch of a new biotechnology facility in Japan, which felt like my first real legacy. I had helped create something from nothing.

When I left Wellcome I went into the contract manufacturing business as operations director of Celltech and stayed there for about four years. The contract manufacturing environment exposed me to lots of businesses and lots of creative people. We had to focus on what was best for the customer, so there was a lot of collaborative diplomacy involved. The people skills I had developed through working in different cultures really came into play.

And then you left the UK for a while?

Yes. I got itchy feet and was offered an opportunity in Europe in 1994. I joined a US company with an operation in Holland, once again putting infrastructure and teams in place to get products out into the marketplace from a new facility.

I came back to the UK four years later – in 1998 – for something quite different. I was asked to help at a start-up business that had some great programs in its portfolio but had lost its way. It ticked all of the boxes for me: I was in at the beginning, it was a real challenge, I got to work with like-minded people and I was exposed to different areas of business. It was probably the best 11 years of my career. We took a business that was on its knees and built something worthy of acquisition in 2008. I feel very proud looking back. Once again, there's a legacy element there; much of what I put in place is still functioning today.

Is there a common thread that ties your experiences together?

I guess something I've learned through my different career stages is that I love fitting the jigsaw together – making sure that it's building the right picture, to deliver a sustainable business. At the end of the day, I'm more than happy to hand it

over to someone else to fully complete or take the business onto the next level once the infrastructure and teams are in place.

So, how did you end up as project director at ABPI?

Well before ABPI, I joined the gene therapy business, Oxford BioMedica. The business was moving into manufacturing and needed someone who could once again fit all the pieces together. I joined the business, established the manufacturing operation, built the operations team, and managed to secure government funding to meet our ambitious business goals with respect to manufacturing. Through the exposure to the gene therapy environment and involvement with government I became involved with a number of advisory and steering groups and when the opportunity arose to champion the MMIP initiative, I could not resist the challenge. It feels like I've almost come full circle and I hope that I can now give something back to the sector. It actually doesn't feel like a job in the traditional sense – it's more of a passion.

What is the strategy of the MMIP?

The strategy is clear; we want to create the right environment to support investment and expansion of the UK's medicine manufacturing sector. People often talk in terms of a collective ecosystem. We want to glue that ecosystem together and provide a clear and positive roadmap for blue-chip companies, SMEs, and entrepreneurs alike.

The MMIP will focus on four key strategic work streams in Technology and Innovation, Regulatory, Skills and Fiscal. If we can start to work collaboratively to address some of these issues, then our sector will go from strength to strength. These are exciting times for medicines manufacturing and I am very fortunate to be part of a sector that wants to make a positive difference in delivering innovative medicines to patients.

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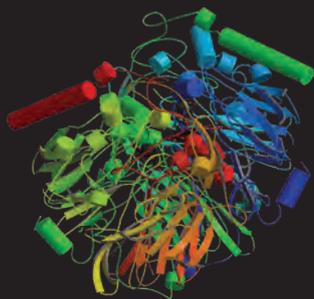
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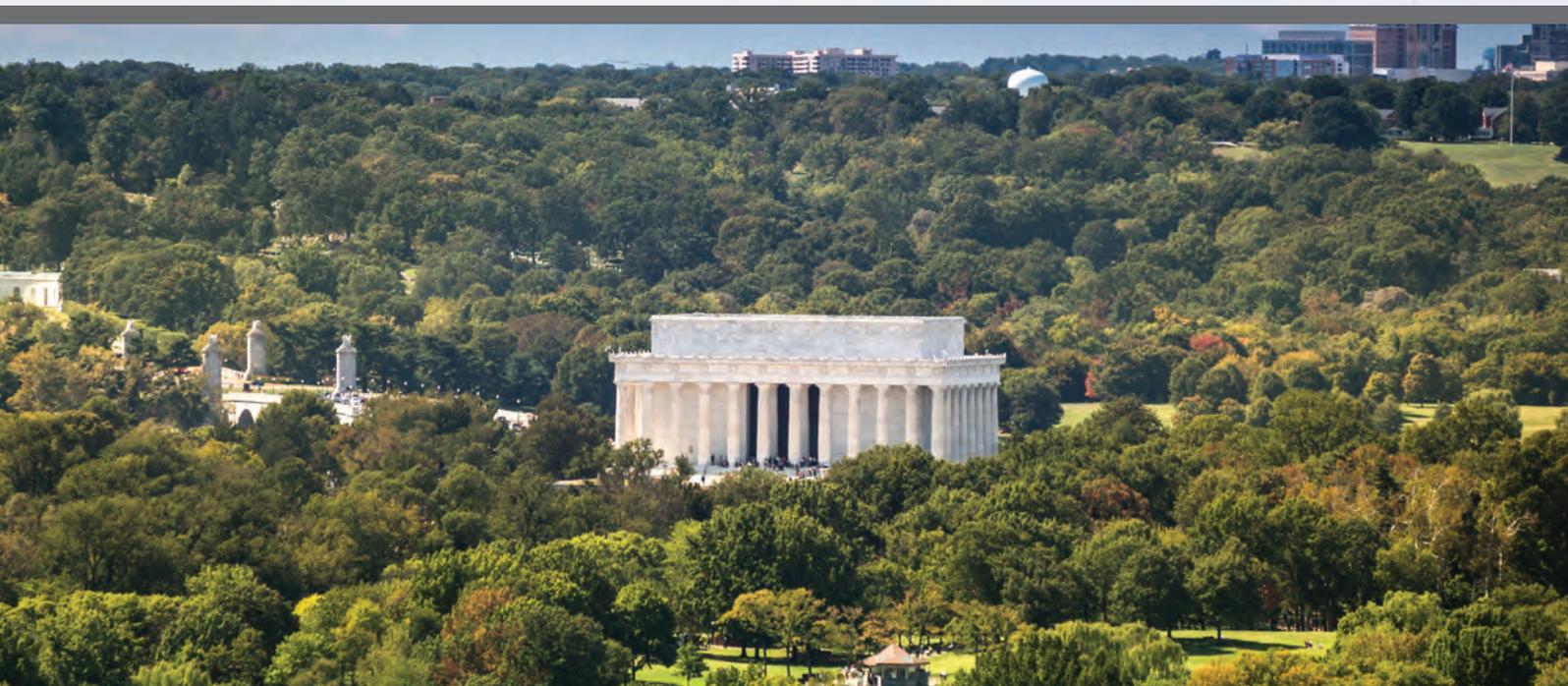
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