JANUARY 2015 # 04

the Medicine Maker

Upfront
Record approvals for rare diseases
14

NextGen
Gaze into the (co)crystal ball
40 – 42

Profession
Rediscovering innovation in 2015
46 – 48

Sitting Down With
Andy Skibo, Chairman of ISPE
50 – 51

Divine Inspiration

By harnessing the awesome power of cellular machinery, metabolic engineering promises a renaissance in manufacturing.

22 – 29

eppendorf

Highly Scalable

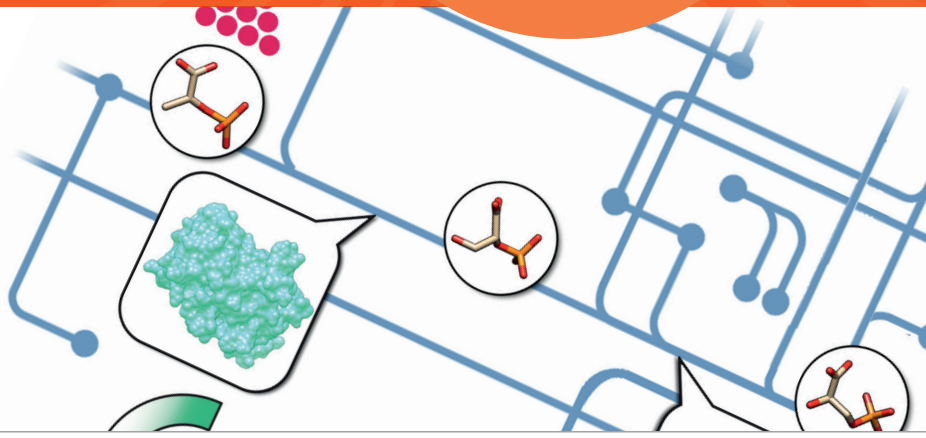
Eppendorf for bioprocess — Solutions that grow with you

With renowned expertise in plastics manufacturing, Eppendorf is proud to offer scalable single-use vessels to be operated with the DASbox® parallel mini bioreactor system, DASGIP® Parallel Bioreactor Systems or New Brunswick™ CelliGen® BLU controllers.

> Proven for animal and human cell lines as well as bacteria and yeasts
> Working volumes of 100 mL to 40 L in cell culture and 65 mL to 1.25 L for microbial applications
> User-friendly set-up for shorter development times and lower operating costs

www.eppendorf.com

Online this Month



The Art of Metabolic Engineering

On page 22, Vikramaditya Yadav explains how metabolic engineering could revolutionize pharma manufacturing. View exclusive illustrations online to find out more about the technology.
tmm.txp.to/0115/yadav-primers

The Final Frontier?

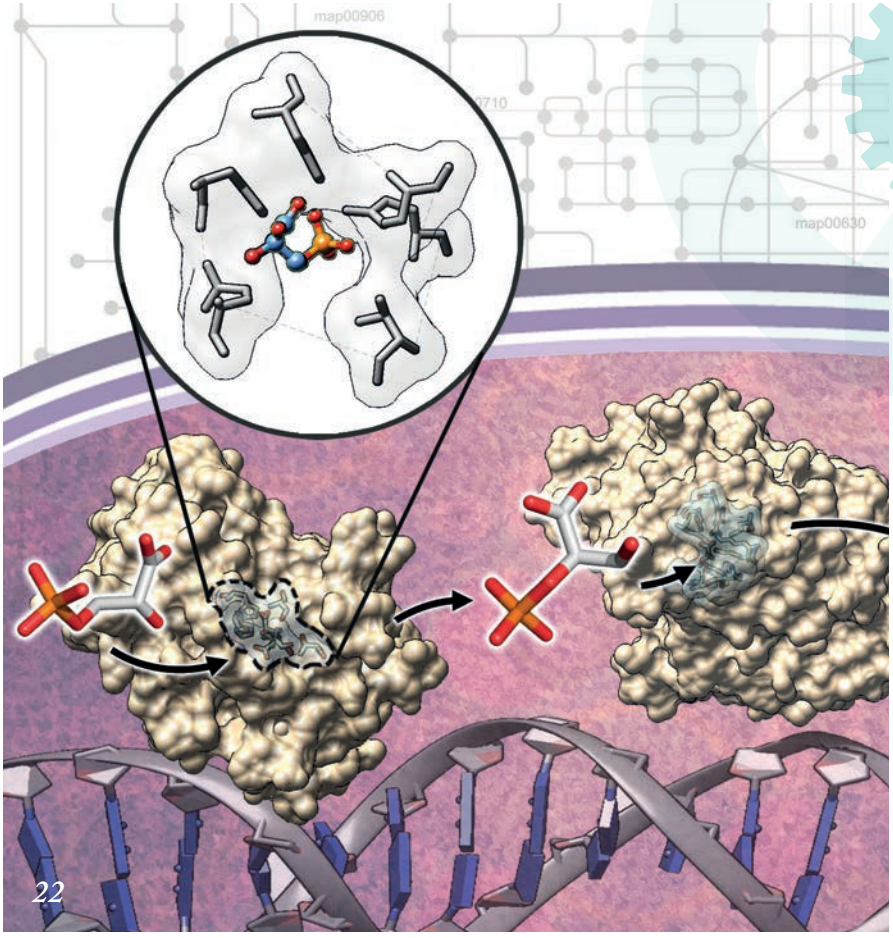
In our last issue we reported on the Galactic Grant Competition that aims to encourage more life sciences research aboard the International Space Station. Although the competition is sadly only available to companies in Massachusetts, it raises some interesting questions about the benefits of drug discovery and development in space. Intrigued? Take a look at our online interview with the Center for Advancement of Science in Space. And let us know if you'd consider taking your work into orbit…
tmm.txp.to/0115/galactic-grant

The Power List 2015 – Nominations Open

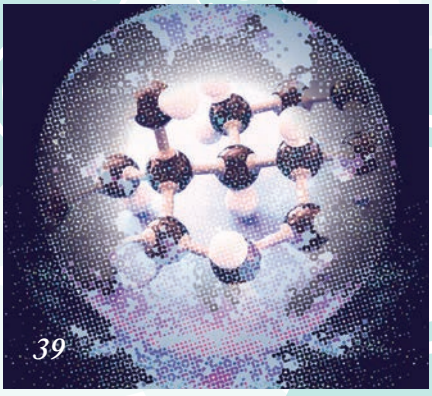
Who are the role models and thought leaders that are inspiring change in the industry? The Medicine Maker Power List 2015 will rank the top 100 most influential people in drug development and manufacture – all based on your nominations. We want to celebrate the passion and commitment of our thought leaders, opinion shapers and unsung heroes. Visit the website or email charlotte.barker@texerepublishing.com to find out more.
tmm.txp.to/2015-powerlist

the Medicine Maker
Power List
2015

Contents



22


39


50

03 **Online This Month**

07 **Editorial**
Power to the People
by **Charlotte Barker**

08 Contributors

On The Cover

This month's cover combines science and art as molecular manufacturing meets The Creation of Adam by Michelangelo.

Upfront

10 Vaccination Innovation

11 Adapting to Adaptive Licensing

12 The 100,000 Genomes Project

13 Disposal Dispute

13 The Eyes Have It

14 Rare Record

In My View

16 Serialization is the next step on the road to our digital future, says **Christian Hay**

17 **Keith Williams** spells out why we must embrace disruptive technology

18 Patients must be at the heart of drug design, says **Richard Fazackerley**

Feature

22 **The Rebirth of Manufacturing?** Is metabolic engineering the ultimate demonstration of continuous manufacturing?

Report

30 **The Medicine Maker × Catalent Applied Drug Delivery Institute**
The Bioavailability Toolbox

Best Practice

34 **How to Embed Excellence**
When it comes to implementing an operational excellence program, where do you start?

NextGen

40 **Crystal Clear Predictions**
Don't get lost in the cocrystal maze; a new model cuts through the complexity.

Profession

46 **Rediscovering Innovation**
Pharma must be brave and boldly go where no one has gone before…

Sitting Down With

50 **Andy Skibo,** Executive Vice President, Operations at MedImmune, and Chairman of the International Society for Pharmaceutical Engineering (ISPE).

the Medicine Maker

ISSUE 04 - JANUARY 2015

Editor - Charlotte Barker
charlotte.barker@texerepublishing.com

Associate Editorial Director - Rich Whitworth
rich.whitworth@texerepublishing.com

Associate Editor - Stephanie Sutton
stephanie.sutton@texerepublishing.com

Associate Editor - Roisin McGuigan
roisin.mcguigan@texerepublishing.com

Associate Editor - Michael Schubert
michael.schubert@texerepublishing.com

Senior Designer - Marc Bird
marc.bird@texerepublishing.com

Chief Executive Officer - Andy Davies
andy.davies@texerepublishing.com

Chief Operating Officer - Tracey Peers
tracey.peers@texerepublishing.com

Publisher - Richard Hodson
richard.hodson@texerepublishing.com

Audience Development Manager - Tracey Nicholls
tracey.nicholls@texerepublishing.com

Digital Content Manager - David Roberts
david.roberts@texerepublishing.com

Traffic and Administration Manager - Vicki Shinks
vicki.shinks@texerepublishing.com

Mac Operator Web/Print - Peter Bartley
peter.bartley@texerepublishing.com

Social Media / Analytics - Stephen Mayers
stephen.mayers@texerepublishing.com

Published by
Texere Publishing Limited, Booths Hall, Booths Park, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK

General enquiries:
www.texerepublishing.com
info@texerepublishing.com
+44 (0) 1565 752883
sales@texerepublishing.com

Distribution:
The Medicine Maker is distributed worldwide through 20,250 printed copies to a targeted European and North American mailing list of industry professionals and 60,150 electronic copies worldwide.
ISSN 2055-8201

texere publishing ltd

innovation loves a guiding hand

Trapped in a solubilization maze? Our enabler, Vaishali Tawde, can help you find the way out. She and her colleagues at BASF work tirelessly to support customers' success. Backed by the resources of the world's largest chemical company, our experts develop next-generation excipients to solve the toughest solubilization and bioavailability challenges. Opening up a whole new world of innovative applications and exciting possibilities.
At BASF, we create chemistry.

Vaishali Tawde,
an enabler in excipients

BASF excipients for solubilization.

Contact us via e-mail at **pharma-ingredients@basf.com**
or visit **www.pharma-ingredients.basf.com**

BASF
The Chemical Company

Pharma Ingredients & Services. Welcome to more opportunities.
Custom Synthesis | **Excipients** | Active Ingredients

Power to the People

Who are the top 100 most influential people in drug development and manufacturing today? That's the question we're aiming to answer with The Power List 2015. But we need your help…

Why list the Top 100? First and foremost, we want to celebrate your achievements, your passion and your pride in your work. You are a fascinating, diverse, brilliant and self-effacing community – your work brings therapies to patients around the world, and we want to put you center stage.

We have seen tremendous progress in recent years. In just this single issue of the magazine, you can see advances in every aspect of drug development and manufacture - from formulation strategies to bring even the most intractable molecules to market, to the development of cell factories for cleaner, greener manufacturing, to ever-increasing safety and efficiency standards. We want to recognize the people who have made all this possible, and who continue to push the field forward every day.

To help us compile this list of the great and good, we want to know who has influenced you. Perhaps it is their groundbreaking research, or their generosity in sharing their knowledge with colleagues. It might be their leadership and business acumen, their commitment to raising standards, or their ability to unite the field behind a common cause. Who are the thought leaders, the opinion shapers and the unsung heroes of the industry?

Of course, we expect to see plenty of senior executives on the list, but we want to throw open the door to academics, regulators, consultants and philanthropists too. We welcome nominations from small molecule and biologic sectors, originator and generic, pharma, biotech and contract organizations, from all four corners of the globe and from any discipline. Have your say on who appears on what we anticipate will be a hotly debated and contested list!

You can nominate as many people as you like – nominate yourself, a colleague or a hero of your field. Fill in the short nomination form at www.themedicinemaker.com or drop me a line at charlotte.barker@texerepublishing.com. Nominations will be reviewed by a panel of judges, who will be responsible for choosing the final 100.

Help us celebrate the people who are pushing the field forward in The Medicine Maker Power List 2015.

Charlotte Barker
Editor

Vikramaditya G. Yadav

As an undergraduate student in chemical engineering at the University of Waterloo, Vikramaditya G. Yadav coveted a career in Alberta's burgeoning petrochemical sector. One evening during his second year, he stumbled upon a copy of Juan Enríquez's 'As the Future Catches You' in the library and was instantly captivated by biological engineering. "My new found passion took me on a wonderful journey that included stops at Sanofi Pasteur and the Massachusetts Institute of Technology, where I received my doctoral degree for a thesis on engineering enzymes and bacteria for synthesis of pharmaceuticals," says Vikramaditya. Now, as an Assistant Professor at the University of British Columbia, he is conducting wide-ranging research in metagenomics, bioenergy, water bioremediation, drug discovery and manufacturing, phytochemistry and Alzheimer's disease.

Vikramaditya discusses the potential of metabolic engineering on page 22.

Duncan Emerton

Duncan Emerton has experience across a broad range of pharma disciplines including R&D, sales, marketing, medical affairs, competitive intelligence, management consulting and business analysis. Duncan currently heads up FirstWord's syndicated reports business, where he's responsible for delivering future-focused research and analysis across a wide range of topics. "My current passion is biosimilars," says Duncan. "I'm a regular presenter and chair at biosimilar-focused conferences, and I've contributed several articles and book chapters on the subject." In his spare time he plays golf and runs The Biosimilarz Blog.

Duncan explains why pharma must rediscover the spirit of innovation on page 46.

Chris Hunter & Rafel Prohens

"I was born in Dunedin in New Zealand, but then lived in Nigeria before my parents settled in Ireland. Following an undergraduate degree in Natural Sciences, I stayed at the University of Cambridge for a PhD in the Chemistry Department," says Chris Hunter. He then decided to revisit New Zealand and took a lectureship in bioorganic chemistry at the University of Otago. He later moved to the University of Sheffield before returning to the University of Cambridge in 2014 as the Herchel Smith Professor of Organic Chemistry.

Born in Catalonia, Rafel Prohens grew up in Mallorca. "I received a PhD in Organic Chemistry from the University of the Balearic Islands and straightaway joined Chris Hunter's group at Sheffield University. In 2012, I founded CIRCE Crystal Engineering, a project to transfer Hunter's approach on the study of intermolecular interactions into technological tools for the pharmaceutical industry." Today, Rafel combines his roles as Scientific Director of CIRCE, Technical Manager at the University of Barcelona, and Research Visitor at the University of Cambridge.

A new dawn for cocrystals is predicted by Chris and Rafel on page 40.

Getting from A to B just got easier

With Provantage® GMP drug production services

Provantage® services give you access to a proven protein manufacturing template and our world-class team of experts who have decades of experience working on more than 180 different molecules. We can help from start to finish:

- Tailor the template to your molecule
- Produce drug substance from 50 - 1250 L at our mammalian GMP facility
- Facilitate tech transfer and implementation to your site

The result? Your molecule moves faster and more reliably into the clinic and then to market.

Contact us today to learn more about Provantage® GMP drug production services.

Fast. Efficient. Less risk.

www.emdmillipore.com/provantage

EMD Millipore is a division of Merck KGaA, Darmstadt, Germany

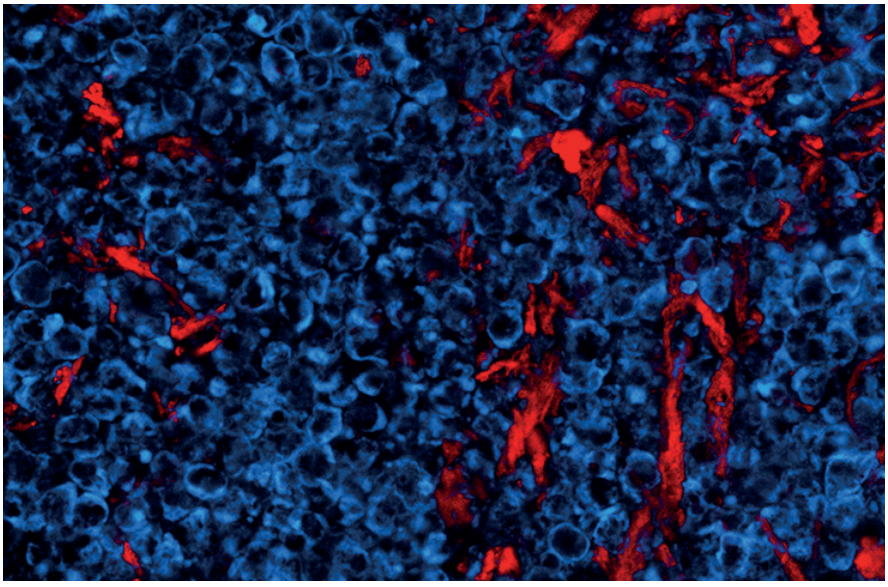
Lit. No. AD1312EN00 Rev. A 11/2014 PS-14-09832-EX

Upfront

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

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

Email: charlotte.barker@texerepublishing.com



Vaccination Innovation

Are vaccines set for a makeover?

Two innovative studies from researchers in Massachusetts demonstrate the creative new approaches that R&D scientists are taking to improve the efficacy – and convenience – of vaccination.

At the Forsyth Institute, scientists have developed a new oral system that utilizes the natural bacteria in a patient's mouth (1). According to Antonio Campos-Neto, Director of the Global Infectious Disease Research Center at the institute, "Commensal non-disease causing oral bacteria are attractive vaccine vector candidates, because they are safe. They are also able to colonize the oral mucosa and they elicit potent mucosal immune responses."

Campos-Neto and colleagues reported their findings in a recent study where Streptococcus mitis was used as the delivery vehicle for immunization against Mycobacterium tuberculosis. The group generated a recombinant S. mitis (using homologous recombination) that expressed the TB bacteria protein – Ag85b. Tests on animals showed that the vaccine was safe and elicited the production of oral and systemic anti-Ag85b specific IgA and IgG antibodies.

"A major hurdle in oral vaccine development is the delivery system itself. In other words, for a vaccine to induce a good immune response it is important that the components of the vaccine stay at the delivery site for enough time to create a physiological inflammation that will in the end induce the immune response. The delivery system, in our case a delivery vector, is a normal component of the oral microbiota – i.e., a "normal bacteria" that is part of the healthy oral microbial flora. This vector, in contrast to many other delivery systems, stays at the site of its delivery (oral cavity), thus circumventing this issue," explains Campos-Neto. "One of our goals was to use an efficacious immunization platform that can be used in developing countries."

Meanwhile at Harvard University, a team has been looking at multidimensional ways to improve on the traditional bolus injected vaccine for applications in cancer and

infectious diseases. They have produced a 3D vaccine made up of microsized rod-shaped microparticles that after injection spontaneously assemble in the body to form a defined 3D scaffold. The macropores formed from the stacking of long aspect ratio micro-rods are big enough for immune cells to infiltrate.

"We showed that we could recruit millions of dendritic cells and program them using various molecules we deliver from the material," says David J. Mooney, one of the authors of the work (2). "A single injection of this technology can elicit serum antigen specific antibody titer that is a magnitude higher than that from traditional bolus vaccines, even after boosting."

"Moreover, we showed that this vaccine can delay the onset of tumor growth for much longer than traditional bolus vaccination," adds Aileen Li, a PhD student at Harvard's School of Engineering and Applied Sciences, who co-led the study alongside Jaeyun Kim, a professor at Sungkyunkwan University in South Korea. "This technology platform is very versatile in terms of material property manipulation and drug delivery. We are excited about its potential in a number of vaccine applications."

Both projects are in the very early stages. Mooney says that the 3D scaffold vaccine platform is currently being tested on various disease models, while Campos-Neto is looking to test the actual efficacy of the oral vaccine with experiments in non-human primates. *SS*

References

1. *N. Daifalla et al., "Commensal Streptococcus mitis is a Unique Vector for Oral Mucosal Vaccination", Microb. Infect. doi:10.1016/j.micinf.2014.11.002 (2014).*
2. *J. Kim et al., "Injectable, Spontaneously Assembling, Inorganic Scaffolds Modulate Immune Cells In Vivo and Increase Vaccine Efficacy", Nat. Biotech. 33, 64–72 (2015).*

Adapting to Adaptive Licensing

EMA's pilot project continues. Is the future of regulation adaptive?

Lynn Baird referred to adaptive licensing as the "future of licensing" in the November issue of The Medicine Maker ("Adapting to the Future of Licensing" [tmm.txp.to/0214/adapting]) and it seems that many companies feel the same way. A recent progress report released by the European Medicines Agency (EMA) shows that 34 submissions had been received as of December 2014 for its adaptive licensing pilot project – Adaptive Pathways.

Adaptive licensing has a more staggered approval process, with the medicine first authorized in a restricted patient population under close monitoring. If all goes well, the marketing authorization can gradually be expanded to new patient populations, with data being accumulated along the way.

The majority of the requests received by the EMA related to anticancer medicines and orphan medicines, and six submissions have now been selected for what the EMA refers to as a 'Stage II meeting', which involves an in-depth discussion with all stakeholders. One such meeting has already taken place and the others are planned for 2015.

After February 28, the EMA will only accept new submissions that are "well developed" and hold potential for "meaningful" Stage II meetings. Specifically, the agency is looking for submissions that are amenable to health technology assessment (HTA) and a real-world data approach, and that carefully consider the indications and populations that would be suitable for initial use of the product. The EMA also handed out additional advice for applicants: don't be vague.

"Applicants are reminded that general statements (e.g., 'a registry will be set up to collect post authorisation data' or 'we anticipate a high level of interest from HTAs') do not provide sufficient elements to evaluate the suitability of an approach for the Adaptive Pathways, and should be avoided when filling the application form," says the EMA report. "Scenario-planning, based on 'what-if' scenarios, is welcome so that multiple pathways can be discussed," adds the EMA.

The report summarizes the EMA's initial experience with the pilot, but a full review of the outcome and impact will be made when at least six products have completed the procedure of parallel scientific advice with HTA bodies. *SS*

Reference

1. *European Medicine Agency, "Adaptive Pathways To Patients: Report On The Initial Experience Of The Pilot Project", EMA/758619/2014, www.ema.europa.eu (15 December 2014).*

The 100,000 Genomes Project

An ambitious UK sequencing project aims to learn more about patients with cancer and rare diseases

The Human Genome Project was declared complete in 2003 to great applause from the scientific community. But then a big question quickly presented itself: how can we use the data? Time to think big.

The 100,000 Genomes Project was launched by Genomics England in 2014 with the aim of sequencing and analyzing 100,000 genomes from patients and their families affected by cancer or rare diseases. We found out more from David Bentley, vice president and chief scientist at Illumina, who is leading a team at Illumina in Cambridge to help bring genome sequencing to the bedside, in partnership with Genomics England.

It can't be as easy as it sounds – can it?

The time is right to do it and the concept is easy to grasp, but we must remember this is the first time in the world that a project of this scale has been attempted. Several countries and organizations have been deliberating on this idea for some time, but the UK is the first to take the plunge. It's difficult being right at the forefront because every problem you come across is new – and you have to solve it.

The technology we're using is Illumina's HiSeq X Ten sequencer but it's not just about instrumentation; the project requires a huge infrastructure to track the samples being collected from hospitals and the regional centers, log all the processes and quality-control steps, and monitor how we analyze the data afterwards. The scale of the 100,000 Genomes Project demands a significant level of process engineering beyond what the original research pipeline has been doing.

How did the project get started?

Almost all disease has some genetic component. Some of it is obvious as the disease runs in families, and some is more complex like the genetics underlying breast cancer. But genetics play some part in almost every disease, which means that we would ultimately have to develop an almost infinite number of different tests to cover all diseases. Instead, the idea behind this project is to sequence the whole genome of each patient and learn how to extract the clinically useful (or actionable) information for each case.

The Human Genome Project promised a great deal – many said early on that it had not delivered on this promise, but I believe people need to understand that it can take a long time to develop the necessary understanding and all the tools needed to make proper use of the reference sequencing. We have a fantastic human genome sequence - it's just that we didn't have the right tools to use it at the beginning.

How has technology advanced since the Human Genome Project?

When I was a PhD student, I did manual sequencing using the Fred Sanger method. I sequenced one piece of DNA in a test tube, and if I wanted to sequence four pieces then I used four test tubes. The number of sequences I did at once was determined by the number of tubes I could handle. Fast forward to the Human Genome Project, and machines were used that could manipulate a hundred fragments at a time. Now, with our technology we can do five billion fragments at once in a single run on one HiSeqX machine.

How difficult is data interpretation?

A genome has three billion bases and between three and four million of those are different between people… so we don't have to analyze everything. What we need to look at are the bases that differ between diseased and non-diseased individuals. With computer systems and software you can then attach meaning to the differences – then you can discover which mutations occur within cancer genes or genes that may cause a genetic disease.

Clearly, it's not always so easy – cancer and many genetic diseases are highly complex, and we know much less about the underlying genetic factors that influence disease onset.

Will the project kickstart R&D in the pharma industry?

Providing pharma companies with access to the Human Genome Project or 100,000 genome sequences is not enough. It is really important also to include clinical information associated with each genome – this is the role of the Genomics England clinical interpretation network that is part of the 100,000 Genomes Project.

What are your hopes?

I really do believe that it will achieve a very long-held goal: introducing precision medicine. Using information from each genome, each patient, and all the results of the 100,000 Genomes Project in aggregate will massively increase the precision with which we understand and diagnose diseases of all kinds, and it will help doctors every day when they make diagnoses and take clinical decisions.

For more information about the 100,000 Genomes Project, visit www.genomicsengland.co.uk

Disposal Dispute

Legal tussles continue over 'drug takeback' law in Californian county

Who should pay for the disposal of unused medicines? The county of Alameda in California has decided to put the financial responsibility for unused medication disposal on drug makers. Based on schemes already applied in Europe and Canada, all manufacturers with products available in the county must fund or establish a local program to collect and dispose of unused prescription medicines, regardless of where the manufacturer is located. Refusing to comply results in a fine of $1000 per day.

Alameda's Safe Drug Disposal Ordinance was approved by the county's lawmakers in 2012, but US industry bodies have been trying to overturn it. At the end of December 2014, the Pharmaceutical Research and Manufacturers of America (PhRMA), the Generic Pharmaceutical Association (GPhA) and the Biotechnology Industry Organization (BIO) turned to the US Supreme Court with a petition to overturn the law. The organizations agree that disposal programs offer health and safety benefits, but they disagree with the premise that drug companies should be forced to pay for it.

"The Ordinance shifts the burden of funding and administering a program solely benefitting local interests onto interstate producers (and, by extension, out-of-state consumers), ensuring that the brunt of the cost falls on outsiders instead of local residents," argues the petition.

This isn't the first time PhRMA, GPhA and BIO have tried to take action, but a previous lawsuit with the US 9th Circuit Federal Court of Appeals failed to reverse the law. *SS*

The Eyes Have It

For the first time, stem cell therapy has been recommended for use in Europe

Ophthalmology has been a big focus for stem cell research in recent years, so it's no surprise that the first stem cell therapy to be approved in Europe will be for use in the eye. In December, the European Medicines Agency (EMA) recommended approval of HHoloclar, a cell therapy produced by Italian company Chiesi, that treats limbal stem cell deficiency, which can cause blindness if left untreated.

Limbal stem cells are found at the edge of the cornea and, in the healthy eye, generate new corneal cells to replace those lost by wear and tear. When limbal stem cells are depleted, often due to an injury, the cornea cannot regenerate and becomes scarred and eroded. The new treatment benefitted from the EMA's orphan drugs program, which allowed the manufacturer to claim several rounds of free scientific advice.

Holoclar is produced from a small biopsy that is taken from an undamaged region of the cornea. Limbal stem cells are extracted from biopsy and cultured in the lab, before being placed back onto the eye, where they regenerate the cornea. The treatment has been shown to improve vision in 80 percent of patients. And because Holoclar uses cells derived from the patient's own damaged eye, there are no concerns about immune rejection or damaging a healthy eye.

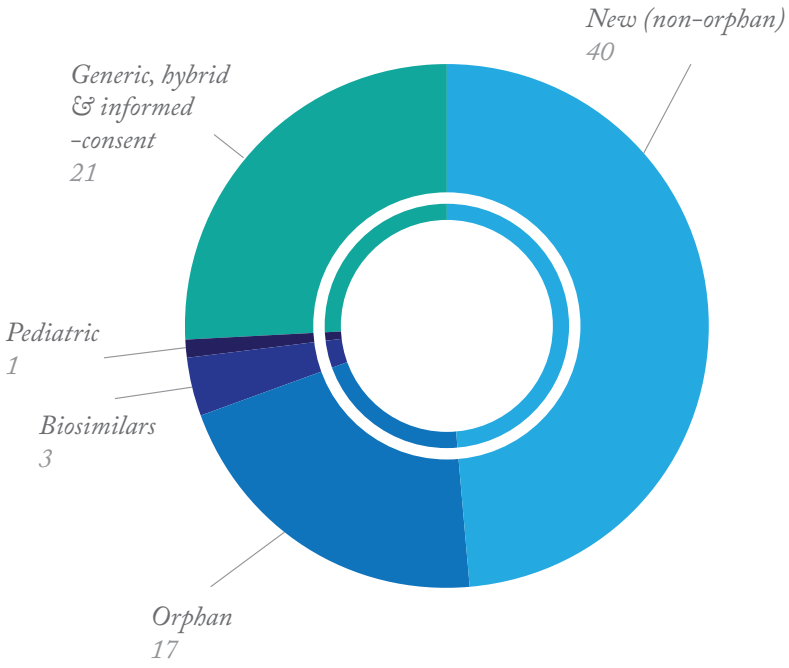
The approval will come as welcome news to several other groups that are working on stem cell therapies for age-related macular degeneration and glaucoma, both common causes of blindness. *CB*

Rare Record

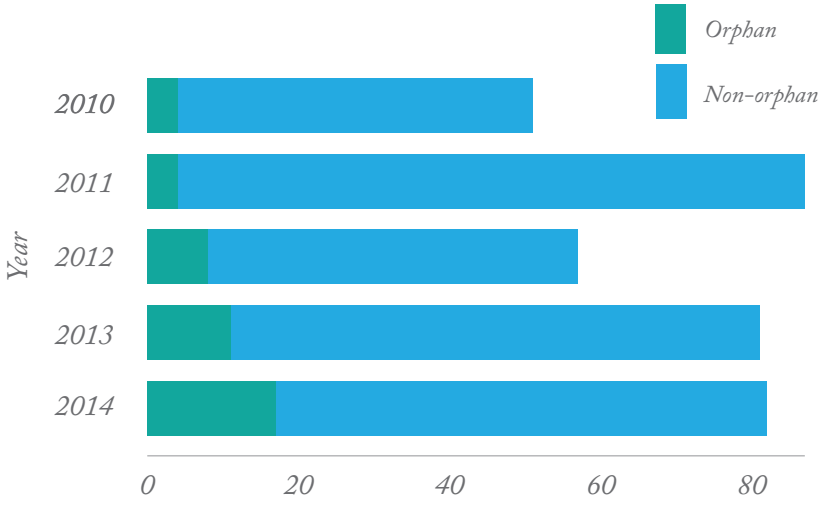
Is research into orphan diseases on the rise?

Judging from recent statistics from the European Medicines Agency (EMA), perhaps so. A record number of positive opinions for medicines for rare diseases were issued by the EMA in 2014: 17 positive opinions (compared with just 11 in 2013), including the first medicine for Duchene muscular dystrophy (Translarna; PTC Therapeutics) and the first treatment for erythropoietic protoporphyria (Scenesse; Clinuvel). 2014 also saw another first, with the EMA recommending a therapy based on stem cells (see page 13). Eight new medicines for cancer were also recommended. Overall, the EMA recommended 82 medicines for approval in 2014. *SS*

EMA positive opinions in 2014 by type (total 82)

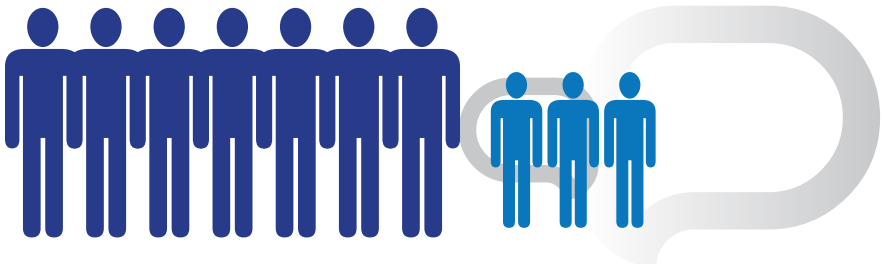


Orphan versus non-orphan positive opinions over time



1 in 2

1 in 2 medicines, either orphan or non-orphan, recommended for approval in 2014, contains a substance that has never been used in medicines before.



7 out of 10

Almost 7 out of 10 applicants received scientific advice from EMA's Committee for Medicinal Products for Human Use (CHMP) during the development phase of their medicine

the Medicine Maker

There are many good reasons to subscribe and it's free to you!

Reason #4: Personal Development

The Medicine Maker can help you reach your full potential, facilitate your employability and enhance your work life in the pharmaceutical and biopharmaceutical sectors. Tailored coverage includes:

- Career planning
- Making you and your team more effective
- Developing strengths and talents
- Mentoring and developing the potential of your staff
- Managing problem employees

Reason #1: Usefulness | *Reason #2: Credibility* | *Reason #3: Style* | ***Reason #4: Personal Development*** | *Reason #5: Relevance* | *Reason #6: Community*

Subscribe free to the print, online, tablet and smartphone versions at www.themedicinemaker.com/subscribe

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

Beyond Barcodes

Serialization will enable our industry to take up its rightful place in the 'Internet of Things'.

By Christian Hay, Senior Consultant, Healthcare, GS1 Global Office, Convenor ISO TC 215 (Medical Informatics), WG 6 (Pharmacy and Medicines Business), Geneva, Switzerland.

It's obvious that "digital" is the key word of the 21st Century. We have instant access to information, devices that connect us to people around the globe, and we even have smart devices monitoring our health. The quantity of information generated and accumulated by digital devices was the stuff of science fiction only one or two decades ago.

What about digitalization involving non-electronic objects, such as medicinal products or medical devices? Welcome to the era of serialization in the pharma industry…

About 40 years ago, GS1 was created to set global standards for product identification within supply chains. Today, our identifiers are used worldwide in various industries, including healthcare. Providing unique item identification was our first task, which resulted in the "EAN/UPC" linear barcode. Electronic catalogues have also been standardized with the GS1 Global Data Synchronization Network (GDSN), which allows trading partners to share information about the items they sell, purchase and ship. This information may include, for example, measurements, product description, characteristics and classification.

From 2015 onwards, one element is going to play an increased role: item serialization, where every item, such as a single packet of medicine, has a unique number. It is an extension of the current GS1 Global Trade Item Number (GTIN), made by appending a serial number to that GTIN.

Leveraging what GS1 has already achieved is key to making item serialization successful. It means ensuring that existing processes that do not require item serialization continue to work: ordering, stock management, shipments, cross docking, and so on. The global use of a single standardized identification system enables access to a considerable variety of products. Now, with item serialization, new processes will be enabled – for medicinal products, fighting against falsification will be a global priority. This requires production lines to be updated to a complex new process; not only does each retail pack need to carry a "unique number", but that number should be aggregated when

"Now, with item serialization, new processes will be enabled – for medicinal products, fighting against falsification will be a global priority."

the retail packs are placed into one carton (which also has to be identified with a GTIN and a pseudo-randomized serial number). The "unique numbers" have to then be populated safely into a regional repository, which will be queried when dispensed(e.g., by the pharmacist).

In the pharma industry, the serialization component will be managed by each manufacturer or marketing authorization holder, using sophisticated algorithms to prevent falsifiers from reproducing sequences of serial numbers. When a very large number of actors is working to make the supply chain safer, an open system of standards is the only way to provide unique identification. In addition, standardized electronic messages exchange information to track the journey of myriad items across the globe and between trading partners, in an interoperable way. In the first stages of implementation, this might be limited to an end-to-end verification system, but the standards to be implemented should be scalable to event tracking. A large-scale pilot project that took place in Sweden in 2009 (run by the European Federation of Pharmaceutical Industries and Associations) provided insight into how this will work in reality; individuals at point of care were able to capture the unique number to look-up the price, manage the stock and query a database in which the unique numbers were verified. The latter process took less than 0.5 seconds in 95% of cases, so it did not delay the dispensation process. Combined with safety features on the packaging, the medicinal product should be safely dispensed to the patient.

Regulators understand that implementing one global supply chain standard is crucial to securing our supply chain. As serialization progresses, trading partners will develop additional benefits from this powerful technology in areas such as business intelligence – which could ultimately benefit patients worldwide.

At the end of the 20th Century, one of the ambitious visions proposed for the new millennium was the "Internet of Things": that is, the capacity for objects to interact and generate new information without human intervention. The Internet of Things is now a reality, and with the first phase of the Drug Quality and Security Act coming into force in the US, and ever-more sophisticated serialization, our pharma industry is increasingly becoming part of this brave new world.

Embracing Disruptive Technology

Big pharma must be more agile if it wants to make the most of the revolutionary advances that will shape the next decade.

By Keith Williams, Managing Director of Formpipe.GxP, Nottingham, UK.

Disruptive technology either displaces established technology, shaking up the industry or standard practice in the process, or it creates a completely new industry altogether. Personal computing, for example, has been disruptive in many ways and has led to other disruptive technologies throughout its adoption.

Disruption seems to occur when there is an aggregation of current technologies, creation of associated processes to adopt them, and people who know how to deploy them. This combination gives rise to a new way of doing things. Large pharma companies are notoriously slow at adopting new technologies; for instance, only now are continuous manufacturing methods starting to be used in place of discrete batch manufacturing.

I think the main factors associated with a reluctance to embrace change are:

- cost of change from an approved process/facility/method/diagnostic
- lack of detailed understanding of the new technology in quality and regulatory groups, and thus an inability to make a sensible assessment
- fear of losing licenses – it is easier to stick with known technologies;
- lack of well-established technology transfer methodology

"I believe that some truly disruptive technology is on the way for the life sciences industry over the next decade. And companies will be forced to adapt."

I believe that some truly disruptive technology is on the way for the life sciences industry over the next decade.

"I see many hurdles that will need to be overcome if these new approaches are to be adopted."

And companies will be forced to adapt.

Computing power has continuously increased according to Moore's law, which predicts that processing speed will double every two years (1). The advent of PCR to amplify DNA, the design of automated DNA sequencers, and an increase in computing power have all combined to create the disruptive technology known as gene sequencing, leading to the characterization of the first human genome in the 1990s (2) for around $3 billion (3). Today, you can have your genome mapped for less than $3,000 (4). That's a one million times cost reduction in 15 years.

The lower cost is significant because it has finally brought the concept of individually tailored medicine within reach. I am not unique in proposing that the next fundamental change to medicine will be the widespread use of treatments tailored for the individual. The 'one-size-fits-all' approach to drug and device development of the past 75 years will surely decrease over time. Better outcomes for the patient will demand personalized treatments that are specific to the patient (or small patient groups categorized by genotype), their symptoms and physical attributes. Meanwhile, the quality and sensitivity of diagnostics are improving such that the diagnostic and the therapy are being developed in tandem to enable detection and treatment in personalized medicine.

Perhaps the dawn of gene therapy could now be beginning to break the horizon (notably, some three decades after it was described as 'the future of medicine' when I was doing my Master's Degree in Biochemical Engineering). Recent advances in clinical trial approaches (again driven by the increase in computing power) and the possibility of creating a 'complete physiological human' with all biochemical processes mirrored 'in silico' (5, 6) should lead to much quicker clinical trials – and replication of the phenotype of a specific individual.

Of course, once specified for the individual, each unique therapeutic molecule needs to be developed, tested and manufactured. And this is where big pharma will have to overcome its fears and commit to both the costs and regulatory uncertainty of creating individual treatments.

As someone who helps life sciences companies stay compliant, especially in terms of new technologies, I see many hurdles that will need to be overcome if these new approaches are to be adopted. As well as further developing the technology itself, we need to work with regulators, encouraging them to understand new technologies whilst still addressing the need for patient safety. We also need to persuade quality and regulatory professionals in pharma to react and respond to new techniques with agility – the same kind of agility that has allowed fast yet controlled development of software over the past decade. One thing is certain; the people and companies who do not fear disruptive technology are those that will prosper from them.

References

1. *Moore's Law, www.mooreslaw.org*
2. *Human Genome Project, www.genome.gov/10001772*
3. *Human Genome Project, "The Human Genome Project Completion: Frequently Asked Questions", www.genome.gov/11006943*
4. *E. Zimmerman, "The Race to a $100 Genome" (25 June 2013) http://money.cnn.com/2013/06/25/technology/enterprise/low-cost-genome-sequencing*
5. *Insigneo Institute, University of Sheffield http://insigneo.org/*
6. *European Commission, "Virtual Physiological Human", https://ec.europa.eu/digital-agenda/en/virtual-physiological-human*

Bright Idea, Dim Design

What's convenient for manufacturers does not always result in a product that's best for patients. In fact, sometimes it's quite the opposite.

By Richard Fazackerley, Technical Director, Finished Dose, Aesica Formulation Development, Nottingham, UK.

A recent report from the Tufts Center for the Study of Drug Development estimated the cost of developing a new drug at $2.6 billion (1) – a figure that has more than doubled in the last decade. Yet despite the huge sums being spent on research and development, the pharmaceutical industry does not always develop products and dosage forms that are fit for purpose.

I have spent a large part of my career

working at the interface between manufacturing and development, bringing new products to market, and I can honestly say that I learn more about product design from patients than from anyone else. There is no question that those working in the industry are involved and committed, but we need to do more to ensure medicines are designed to meet the needs of patients, not industry.

Firstly, it's important to recognize the most obvious fact: patients, by definition, are not well. It's amazing how often this fact is overlooked. As an example from my own life, my late father received medication for the treatment of two chronic conditions that require a strict regime of medication: Parkinson's disease and Alzheimer's disease. My father's fine motor skills were poor but a number of the tablets prescribed were small and supplied in blister packs. Simply removing a tablet from the pack and taking it was a daily challenge and, judging by the number of escaped tablets found under the toaster in the kitchen, not always successful. Oral solid dosage forms like tablets or capsules are popular with patients and manufacturers alike, but in the case of my father – and many other patients like him – a different dosage form, such as a larger orally dispersible tablet, would increase medication compliance and make their lives easier.

Another example comes from a frustrated colleague who couldn't understand why a member of the development team kept asking if the product was "compatible with pureed apple" at every development meeting. The reason behind the seemingly odd question was simple: the most common administration route for the target patients, many whom were elderly and suffered from swallowing difficulties, was co-administration with food. In such cases, a granule or powder formulation is far more appropriate or alternatively an oral suspension may work, depending on the compound characteristics.

If manufacturers do not meet the needs of patients, they will often take matters into their own hands. I never cease to be amazed by how far patients will go to overcome some of the design shortcomings in pharmaceutical products. Simple solutions include grinding tablets or opening capsules, which may inadvertently undo a lot of the good work done in development or even be dangerous in some cases. In another example, an elderly patient used to ask visitors to open her child-resistant pill bottle because it was too difficult for her to open. But she also asked them not to close the bottle. Her strategy was to leave the bottle – a month's supply – open until empty. Bang goes the in-use stability study! If the food industry can supply artificial sweeteners in simple push dispensers, why is the technology not adopted more widely for pharmaceutical products? There are obvious challenges to overcome, such as child resistance, but the technical solutions are available if we are willing look.

"There is no question that those working in the industry are involved and committed, but we need to do more to ensure medicines are designed to meet the needs of patients, not industry."

We, as an industry, need to more carefully consider patient needs and start moving away from decision-making that is based solely on what is most convenient from a manufacturing or development perspective. And that's a big challenge. A standard round bottle is great for production because it removes the need to control orientation, but a square bottle would be easier for patients to handle. I know that meeting patients' needs is not always easy, but it's our job as manufacturers to innovate and come up with solutions, even if that means investing in new technical systems or hiring new expertise.

The way forward for us as a manufacturing industry, and some of us are already on this journey, is to better understand the day-to-day reality for patients, but also for care-givers and medical professionals, and adapt our operations to the realities we find. No doubt there will be challenges and some of our strongly held beliefs and solutions will need to change, especially as we move towards more personalized medicines and away from the historically successful blockbuster model.

Good end-to-end product design can truly enhance the patient's experience and compliance – and it can offer significant benefits for the developer. In fact, the right combination of drug, dosage form, device and packaging can be life changing for patients.

How do you know if you've got it right? Don't second guess – ask the patient!

Reference

1. *Tufts Center for the Study of Drug Development, "Cost to Develop and Win Marketing Approval for a New Drug Is $2.6 Billion", http://csdd.tufts.edu (18 November 2014).*

Product Showcase

Sponsored Section

Aptar Pharma 'Bag-on-Valve'

Aptar Pharma announces the re-launch of its Bag-on-Valve (BOV) activities in its Radolfzell manufacturing site

The fully refurbished Radolfzell (Germany) site constitutes Aptar Pharma's expert center for BOV systems for pharmaceutical applications. After substantial investment, the 2,300 m^2 production area is equipped with new injection molding machines and state-of-the-art assembly lines to comply with the increasing demand from a challenging market.

Aptar is a pioneer in the development and manufacturing of this environmental-friendly dispensing technology. Aptar Pharma's Bag-on-Valve technology supports pharmaceutical products with major benefits such as better use, better preservation and better product protection. Aptar BOV systems, meticulously developed over a number of years, are widely used by major multinational companies.

Aptar Pharma is the AptarGroup business segment dedicated to the evolving needs of biotechnology, healthcare and pharmaceutical companies with innovative drug delivery solutions. We are the worldwide leader in nasal spray pumps for Allergic Rhinitis, Nasal Decongestant and Nasal Saline, and worldwide leader in metering valves used in pMDIs for treatment of Asthma and C.O.P.D. With a strong focus on leveraging innovation to provide patient-focused solutions, we allocate a substantial amount of our annual revenue to research and development. With manufacturing sites in Argentina, China, France, Germany, India, Switzerland and the U.S.A. we can serve the pharmaceutical industry market worldwide. We offer a full range of added-value services that include customized solution development, research and laboratory support, and a dedicated regulatory affairs department. Our sales force and technical experts provide customers with global support.

Aptar pharma

For more information contact us at: aptar.com/pharma/contact

Aptar pharma

aptar.com/pharma

BAG ON VALVE

Product integrity granted by technology

- Ultimate protection of content
- Easy to use and highly convenient
- Manufactured to meet highest standards

Delivering solutions, shaping the future.

The Rebirth of Manufacturing?

In today's aggressive, cost-cutting climate, the desire to switch from batch to continuous manufacturing is strong. As pharma companies embark on prolonged innovation cycles in an attempt to deliver the higher volumes and reduced costs of continuous manufacturing, it might surprise many that the technology they seek already exists.

By Vikramaditya G. Yadav

"This is the book for starting the next century of engineering." High praise indeed, especially when it comes from Marvin Minsky (1), one of the world's most respected sages of cognitive science and artificial intelligence. What's even more astonishing about K. Eric Drexler's book, "Nanosystems: Molecular Machinery, Manufacturing, and Computation," published in 1992, is that it was actually his PhD thesis at the Massachusetts Institute of Technology. The book is remarkable not least because of its bold predictions about what he calls 'molecular manufacturing' and its capacity to transform modern society by replacing current industrial operations with next-generation processes that occupy a negligible footprint, consume fewer resources, are pollution-free and deliver significant improvements in production costs and material quality (2).

The factory in a box

Drexler describes molecular manufacturing as the process of continuously bonding molecules together to produce larger structures, ultimately assembling components whose sizes and complexities range between that of a spatula and an airplane. Bonding is controlled and directed by so-called molecular assemblers, which resemble the machines found in factories today. Drexler packages this vision as '3D-printing perfected' – nanofabrication engines that are quintessential factories-in-boxes (3) – and promises giant advances in manufacturing, miniaturization, materials and computing, as well as solutions to some of society's greatest challenges, including disease and climate change (4).

There is no doubt that Drexler is a visionary and a consummate author. However, when scientific ideas run the risk of being confused for science fiction (Drexler himself raises the example of the Star Trek replicator (3) as the antithesis of his ideas), controversy is often not far behind. In the case of molecular manufacturing, it was Richard Smalley – recipient of the 1996 Nobel Prize in Chemistry for his role in the discovery of buckminsterfullerene, no less – who took strong exception to the idea. Smalley argued that the only way molecular assemblers could synthesize a practical amount of product was if they could self-replicate and, were this to occur, these 'nanobots' would gravely threaten humanity's existence (5). However, in the same article, Smalley went on to extinguish all fears of a nanobot-led invasion by citing what he perceived as two fundamental limitations of the assembler – 'fat fingers' and 'sticky fingers'.

To understand Smalley's criticisms, it is helpful to visualize the molecular assembler as a collection of flexible appendages. Since the appendages themselves are also composed of molecules, it is inevitable that the size of these constituents may exceed that of the molecules being fused together – a scenario that becomes

particularly relevant at the start of an assembly cascade. As a consequence, the appendages might not be dexterous enough for atomically or molecularly precise fabrication, much in the same way a person with fat fingers might struggle to type long sentences on smartphones with small screens. Atomic-level attractive forces between the appendages and the substrate molecules could also interfere with the fabrication process – a situation that is akin to making origami with gluey fingers. What a mess!

Needless to say, Drexler did not take too kindly to this criticism, and, in a strongly worded rebuttal (6), cited the example of the ribosome, a biological molecular assembler that does not suffer from either fat or sticky fingers. In fact, so efficient is the ribosome that the bacterial version of this incredible machine stitches together between 12-21 amino acids each second (7). Cornered, Smalley swiftly corrected his stance. However, if you believe that this clash of titans had reached a respectful conclusion, you would be sorely mistaken (8).

While the Nobel Laureate did concede that a machine such as a ribosome is indeed capable of precise fabrication, he raised doubts regarding the capacity of Drexler's nanobots to exhibit the same degree of control and self-repair as a ribosome. Smalley was also unconvinced about the ability of biological systems to perform non-aqueous chemistries or synthesize inorganic species, such as silicon, or produce materials of construction, such as steel and concrete.

Smalley does not seem to have been an avid follower of developments in the life sciences. In any case, he was certainly oblivious to biomineralization (9). Perplexingly, though, Drexler responded to the latest batch of criticisms by explaining that his vision for molecular manufacturing is strictly mechanical and that production will be achieved exclusively with the aid of computer-controlled, desktop-scale nanofactories. Alas, Smalley's demands of "show me the chemistry" had been met with a pseudo-philosophical "just wait, it's imminent", and the debate began fizzling towards an insipid end.

Nevertheless, of all the surprises thrown up by the debate, the one that stood out the most was the low opinion that Smalley and Drexler shared of biological manufacturing platforms. Even after all these years, Drexler's views have not changed in the slightest. Arthur C. Clarke – one of the greatest science fiction writers – said it best: "If an elderly but distinguished scientist says that something is possible, he is almost certainly right; but if he says that it is impossible, he is very probably wrong."

Metabolic engineering

At the outset, let us re-imagine the cell as a highly connected and well-regulated network composed of a large number of chemical reactions, wherein atoms are sequentially added, removed or exchanged from a molecule as it proceeds through the network. Each reaction is catalyzed by a unique enzyme, which itself is a product of a specific gene. A metabolic network, therefore, is a biological analogue of Drexler's molecular assembly line – a true microfactory. Each enzyme retains its role of a biological machine, and the genetic make-up of the cell is equivalent to the blueprint of the factory floor. Similarly, a metabolic pathway is simply a sequence of interacting machines.

Now, if one were to express an additional copy of a specific gene – altering the factory's blueprint very slightly – the presence of duplicate machines executing the same task would increase the productivity of that particular step. Since no two biochemical reactions are the same, increasing the productivity of one machine in the step could have several possible outcomes. The change could serve to increase the productivity of subsequent machines in the assembly line if these machines are operating below their maximum capacities, meaning that the rate of movement of material through the pathway – a quantity that is termed as 'flux' – increases as a whole. In the converse scenario, if the downstream machines are already functioning at peak capacity, the stock of product produced by the machine in question will begin to grow.

Regardless of the outcome, owing to the high degree of connectivity within the network, manipulation of a single step in the network will spawn system-wide perturbations that greatly alter the intracellular concentrations of several metabolites. Similar effects will also be observed when genes are deleted or manipulated by modifying their sequences, or when foreign genes are introduced into the genetic blueprint. In the latter two scenarios, the genes will encode novel enzymes that synthesize altogether new products by siphoning away atoms destined for native metabolites.

Altering the genetic make-up of a cell to achieve heightened or entirely new production of a molecule is defined as metabolic engineering, and operational decisions such as whether a gene should be deleted or overexpressed – and if it is overexpressed, by how much – are governed by the stoichiometry, kinetics and regulation of the pathway of interest. Therefore, metabolic engineering combines deep understanding of metabolism, biochemistry and molecular biology with the rigorous quantitation of fluxes (10). Since microbial metabolism is easier to manipulate than cells of higher organisms, most practical demonstrations have been made in microorganisms, such as bacteria or yeast. However, applications involving higher organisms are becoming increasingly common. Like the idea of 3D nanoprinting, the seeds of metabolic engineering were sown over two decades ago. However, while the former has remained a fringe idea, metabolic engineering has spawned global industries such as biofuels and biochemicals manufacturing that rake in over $200 billion dollars each year.

To his credit, Drexler did agree that ribosomes and enzymes are extremely efficient molecular assemblers. He just wasn't

sure if these biological machines could ever be employed for synthesizing usable materials beyond common biochemicals, let alone suggest how they could be deployed for next-generation, sustainable manufacturing. Fortunately for us, recent innovations in analytical chemistry, genome sequencing and assembly, and bioinformatics, as well as quantum improvements in the tools of molecular biology have not only brought to light the vastness and staggering diversity of nature's biocatalytic repertoire (11-13), but have also greatly expanded our ability to harness these chemistries for societal benefit (14-15). As a consequence, we can finally contemplate employing metabolic engineering as a meaningful manufacturing platform in industries whose scale and impact comfortably dwarf the biofuels and biochemicals sector.

Greener pharma

The prospects in store for the trillion-dollar pharmaceutical industry are particularly exciting. The vast majority of manufacturing processes in the pharmaceutical industry comprise energy- and resource-inefficient batch operations, and these processes generate, on average, anywhere between 25 and 100 kilograms of waste for every kilogram of product (16). If you were curious, the oil industry generates less than a tenth of this amount of waste per kilogram of product. Who would have thought that oil refineries would stack up favorably against another industry when it came to impact on the environment!

Examples of pharmaceutical companies closing down manufacturing operations because waste disposal costs are overtaking the selling price of the product are becoming increasingly common (for example, DSM shut down manufacture of phloroglucinol, a therapeutic agent used to treat gastrointestinal disorders). There is a clear and compelling opportunity to improve the efficiency of manufacturing processes by transitioning from batch to continuous operation.

In light of some of the aforementioned scientific and technological developments, metabolic engineering is arguably best placed to deliver the revolution in continuous API manufacturing that the industry is so desperately seeking. As the pharmaceutical industry currently spends roughly a quarter of its annual revenues on manufacturing (17), the shorter production times, higher yields, lower consumption of catalysts, solvents, reagents and energy, lower waste generation and enhanced safety of continuous processes could, according to one estimate, translate to greater than 10 percent growth in annual revenues (18-20).

And there's another advantage of using metabolic engineering for production of pharmaceuticals – even the quality and safety of drugs could vastly improve (21). Who needs bacteria to build car engines if they can revolutionize medicine making by churning out better drugs more rapidly and efficiently than ever before?

A typical pharmaceutical manufacturing process can be divided

Sustainable Scale Up

Professor Bernhard Palsson is CEO of the Novo Nordisk Foundation Center for Biosustainability at the Technical University of Denmark, which aims to solve some of the scientific and engineering challenges of large-scale metabolic engineering. We caught up with Palsson to find out more.

What is the goal of the Center?

The Center is the first large-scale research operation that is solely focused on the design, construction and testing of cell factories. The creation of microbial production strains is often very expensive and time consuming – around $50 million and five years. Our goal is to cut those figures to less than $20 million and two years. To do that, the whole center is organized around an iterative design workflow, so that we focus our resources on the current rate-limiting step in the process.

What are some of the most exciting ongoing projects?

There are a couple of pathways that generate compounds important to human physiology, like serine, adrenaline, L-Dopa, melanin, serotonin, nicotine and caffeine. The Center has an exciting project underway to build these pathways into E. coli or yeast, so that we can make any of these compounds in any quantity we like, at an acceptable price.

In the field of protein engineering, one of our scientific directors, Henrik Clausen, has mapped out an engineering platform for specifying glycans on IgG, produced in CHO cells. By customizing glycosylation in the CHO cells that are used to produce IgG, there is potential to improve product homogeneity and therapeutic efficacy.

Where do you think the field is heading?

Taken together, biosustainability efforts for these compounds could have a huge impact on the world's economy – five percent of the world's GDP comes from chemical or pharmaceutical manufacturing. At the Center, we have been trying to determine how many of the tens of thousands of commercially available chemicals can be made biologically, and it appears that it is a very sizeable fraction. The combination of basic research into metabolic pathways and host cell optimization for effective scale up is likely to make enormous inroads into the manufacture of biochemicals and pharmaceuticals over the next decade or two.

into two distinct stages – API synthesis and drug formulation. Purified API is produced in the first stage via an iterative sequence of reaction, separation and purification steps. The API is then suitably formulated during the second stage to yield the finished dosage form. Since nearly 80 percent of pharmaceutical products in the market today are tablets, the product from the first stage is often in a dry, crystalline form. Tablet formulation commences with milling of the API crystals to form a fine powder, which is then blended with excipients and mixed with water to produce wet granules. Drying, tableting and coating follow suit, and the manufacturing process culminates with packaging of the tablets for distribution and sale.

Of all the steps listed above, only milling and tableting currently happen continuously. Clearly, the scope for improvements in the pharmaceutical manufacturing chain is immense. Innovations have indeed occurred, notably in processes that comprise the second stage. For instance, the use of continuous crystallizers, mixers and blenders, and granulators are slowly taking root, and Novartis recently demonstrated continuous operation of the entire second stage of the manufacturing process for Diovan, a drug used to treat high blood pressure and heart disease, at the pilot scale (22).

On the synthesis front, however, the situation is less encouraging. Seventy percent of all reactions that are employed for synthesizing APIs are still undertaken in batch mode (23). Several companies have started experimenting with the use of continuous flow reactors (CFRs), and a number of important chemical reactions have successfully been adapted to the continuous flow format – even at the pilot-scale (24). However, CFRs do not handle solids particularly well and are not suited to multiphase reactions, which has greatly restricted the applicability of flow-based synthesis (nearly two-thirds of the reactions in API syntheses use either a solid reactant or catalyst, or yield a solid product). It is clear that improvements in API synthesis have not occurred at the same rate as they have in solids processing, and it is here that metabolic engineering has a key role to play.

The solution?

API synthesis is an iterative process involving multiple reactors and separation equipment. Briefly, one or more raw materials are fed to the first reactor in the sequence along with the requisite reagents, solvents, catalyst and energy. Following completion of the reaction, the 'product' – namely, the first intermediate in the synthesis scheme – is purified from the reaction mixture using one or more separation processes, such as filtration or solvent extraction. More often than not, though, the solvents and reagents that are employed in these steps are noxious substances, and large quantities of these materials – not to mention energy – are consumed before a small amount of the intermediate is produced. The first intermediate is then mixed with a different set of reagents, solvents and catalyst in the second reactor, where it is eventually converted to the second intermediate. This sequence of reaction–separation steps continues until the final API is synthesized. Then, the API is crystallized and dried, and later sent to the formulation unit for production of the finished doses.

Now, in the very same process train, imagine a situation wherein no harmful solvents or reagents are ever consumed, and atoms in the raw material supplied to the first reactor are precisely rearranged to produce the first intermediate without ever requiring the temperature of the reaction mixture to rise beyond ambient conditions. The one-to-one conversion of raw material to the first intermediate also obviates the need for any purification. Next, imagine that the first intermediate shuttles over to the next reactor without any expenditure of energy and then undergoes

Pioneering Pathways

Researchers around the world are working to find more sustainable ways of producing plant-derived drugs. We spoke to Jay Keasling, Professor at University of California, Berkley, about his pioneering work on the malaria drug artemisinin, which has been described as the "poster child for synthetic biology".

What makes artemisinin a good target for metabolic engineering?

It's a molecule that has already been approved for the treatment of malaria and is widely used. It's derived from the Wormwood plant, which is not difficult to grow, but the production times are long and it has been difficult for companies to predict demand. Coupled with unpredictable crop success, it's been a challenging drug to source and a lot of it is needed. Finally, we had been working on chemicals that were in the same compound family as artemisinin, so we knew it should be possible to make it.

How did you go about synthesizing the drug?

Several of the genes encoding the metabolic pathway for artemisinin were already known, but some were not; the first job was studying the plant to find those enzymes. That was challenging because plants have a huge number of genes. To find the single gene responsible from 50,000 is a big deal – especially 10 years ago when we started – we didn't have the high throughput sequencing technologies we have now. Once we had the pathway, we tried it out in both E. coli and yeast,

yet another precise, reagent-free rearrangement to form the next intermediate. This sequence of 'clean transformations' continues until the API is synthesized. Sound familiar?

In nature, cheap and abundant carbohydrate-based raw materials are continuously transformed to APIs within a single cell, and what was once an extended cascade of reaction and separation steps is done away with and replaced by a configuration comprising a single reaction–separation step. The synthesis of taxadiene, an intermediate in the taxol biosynthetic pathway, perfectly encapsulates the jaw-dropping efficiency possible. The most efficient chemical synthesis of taxadiene reported to date involves 18 reaction–separation steps (25). The overall yield of the process is a mere 0.21 percent – that's one kilogram of product for every 476 kilograms of raw materials. Biosynthesis of taxadiene, in comparison, involves just four reactions. When a strain of E. coli was simply fitted with the four biosynthetic genes without making any other modifications, the strains produced taxadiene at yields of 0.68 percent and 0.85 percent (on a gram of product per gram of glycerol basis) in two milliliter and one liter cultures, respectively (26). The theoretical yield of taxadiene on glycerol is 11.625 percent, while on glucose, it rises to 20 percent. Implementation of the complete toolbox of metabolic engineering could improve the production of taxadiene nearly a hundredfold over the competing chemical route.

The API itself can be extracted from the culture broth using continuous countercurrent chromatography (27), followed by purification and crystallization to produce the bulk API. Combining such metabolic engineering-based synthesis schemes with a continuous formulation platform similar to Novartis' Diovan process will unquestionably deliver quantum leaps in the atom and energy economies of pharmaceutical manufacturing (28).

The big question

What is the range of products that can be manufactured? Well, this is where metabolic engineering arguably provides its greatest value; the success rate of a conventionally synthesized drug candidate is one in 100,000; on the other hand, one in every 350 natural products that are screened for drug activity eventually makes its way to market. There's a good reason for the nearly 300-fold difference between the success rates of synthetic chemicals and natural products – the latter typically have more chiral centers, rings, oxygenated substituents, and solvated hydrogen-bond donors and acceptors, which reduces the entropic costs that these molecules incur during binding to drug targets. Unsurprisingly, natural products make up well over half of the modern pharmacopoeia, despite the industry tapping into only a small fraction of this roughly 170,000-strong pharmaceutical treasure chest (29). Predictably, companies are eager to increase their efforts in sourcing natural products for screening new drugs, but their best intentions have been put on ice because of insurmountable difficulties associated with procuring natural products. Among others, the supply of source material from which the natural product is extracted is acutely prone to seasonal and environmental variations, the material itself is inconsistent in composition and quality, and extraction yields are often infinitesimal.

However, with the advent of metabolic engineering, the equation is finally shifting back in favor of natural products. Recent investigations into natural product biosyntheses have revealed that these complex molecules are assembled programmatically by pathways that are combinations, permutations and mutations of only a handful of enzymatic reactions. In other words, altering the order, number and cross-talk between the biological machines in the cellular microfactory, or minutely tweaking them, could provide access to a staggering collection of natural products,

and found yeast to be the most effective. The first 1.7 million treatments made using this method were shipped in August. It feels great when something you have worked on benefits people.

Where has your research taken you since then?

The power of metabolic engineering is that once you have built a platform like the one for artemisinin, then it's not so difficult to make a few changes to the pathway and make related compounds. It turns out that the same compound family as artemisinin also includes molecules that can make diesel, jet fuel and even fragrances.

We are also continuing our work on pharmaceutical applications. There's a molecule called prostratin, derived by healers in Samoa from the bark of the mamala tree, and used to treat viral infections. Ethnobotanist Paul Cox came across prostratin while in Samoa looking for an anticancer drug, and it was found to have possible applications for HIV therapy. One of the big problems with HIV is that you can kill the active virus, but not the latent phase. By activating the virus, prostratin could allow antiretroviral therapies to eliminate that reservoir. The drug is now approaching clinical trials, and we are working on determining the metabolic pathway involved, to find a reliable production method.

There are drugs that have been abandoned at clinical trials because the drug simply couldn't be sourced in sufficient quantities from a natural source. Metabolic engineering gives us a method to produce drugs that we otherwise couldn't.

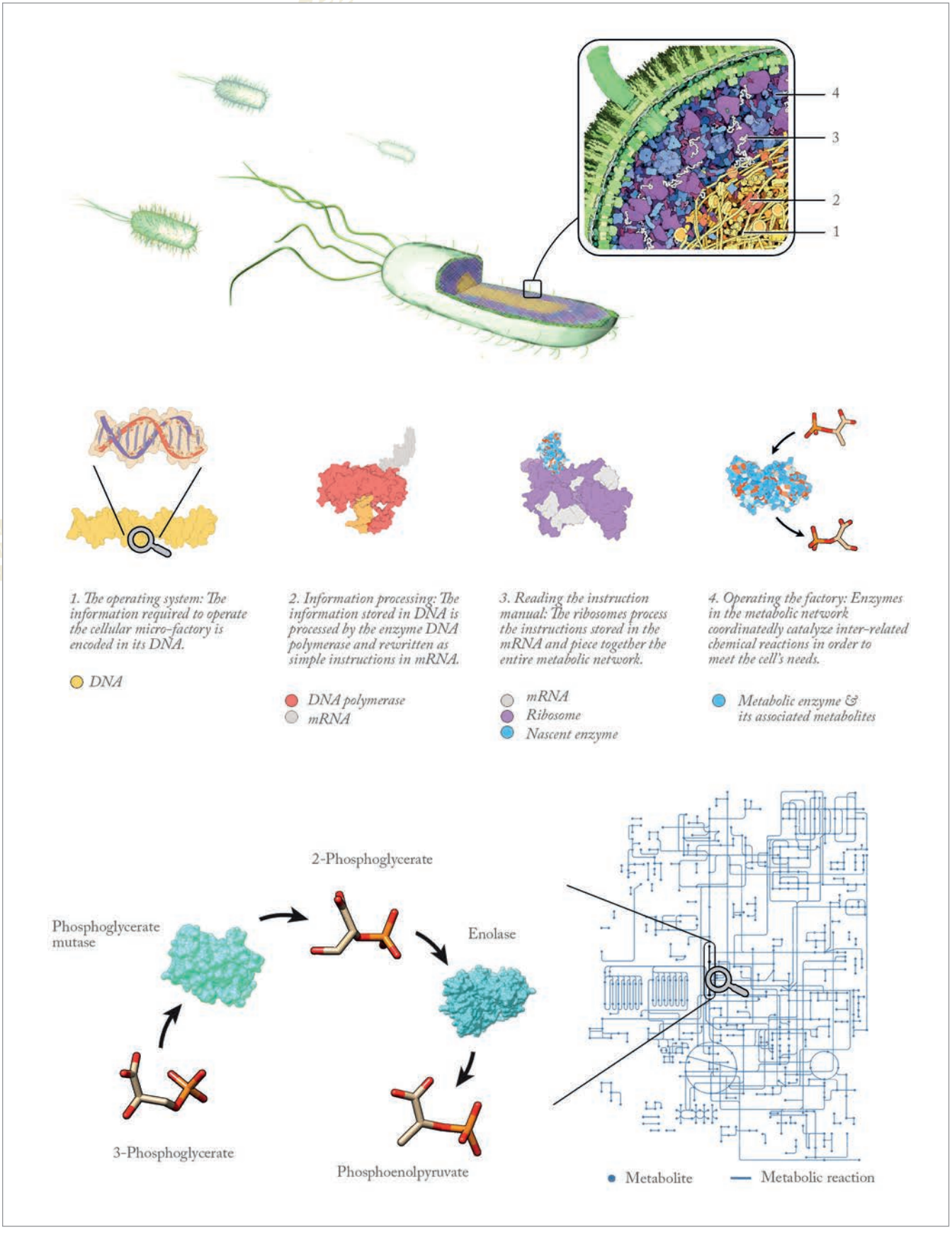


Figure 1. A glimpse into the inner workings of a bacterial cell.

instantly transforming metabolic engineering into a tool for drug discovery. There are other benefits too, such as ease of scale-up. In order to go from gram-scales to ton-scales, one simply has to use a larger fermenter! The footprint of a manufacturing facility based on metabolic engineering is also considerably smaller.

The big challenges

So why isn't metabolic engineering in widespread use in the pharma industry? There are two stumbling blocks. The first is a general lack of good tools. The tools used for manipulating a microbial host's metabolism are not universally applicable. Indeed, they are specific to only certain pathways or products. The lack of transferability of the majority of tools and techniques between hosts, in turn, can be attributed to an incomplete understanding of the regulatory mechanisms in the cell (more on that below). Clearly, there is an acute need for transferable tools and techniques that can characterize and manipulate host regulatory mechanisms to control heterologous over-production of natural products and other secondary metabolites.

Second, there are some significant technical and knowledge roadblocks. Because most natural products are components of the immune and defense systems of their host – and because an organism's evolutionary fitness is contingent on its ability to synthesize that otherwise rare molecule – the vast majority of biosynthetic pathways comprise enzymes that act on several substrates and/or catalyze the formation of multiple products. And that implies that the pathways are actually highly branched, possibly synthesizing several products. The paclitaxel biosynthetic pathway, for example, generates well in excess of a hundred products. As natural product biosynthetic pathways are quite long, the dissipation of intermediate molecules to competing chemical reactions at each step amounts to inordinate losses in the overall yields. Enhancing the substrate and product fidelities of dissipative enzymes is now an urgent problem in metabolic engineering and biocatalysis. Unfortunately, the established method for modulating the activity of an enzyme (which involves selecting similar examples in nature as starting points for modification using mutagenesis or directed evolution) is not applicable to the current scenario. More elaborate structure-guided approaches are required. However, not only is this a very long and involved process, but even in the event that the characteristics of every single enzyme in the pathway are eventually improved, it is uncertain whether simple microorganisms, such as E. coli, will be able to express such a large collection of enzymes without grave physiological stress.

Diversity-oriented biosynthesis presents an entirely new challenge for metabolic engineers, and it is apparent that synthesizing an advanced intermediate that acts as a gateway molecule for target-oriented chemical synthesis is a more viable alternative. Not only would the number of enzymes be significantly more tenable, but such a semi-synthetic manufacturing process would also take advantage of the core competencies of both metabolic engineering and synthetic chemistry.

Despite the hurdles, progress has been rapid in recent years, with groups all around the world making huge strides (see sidebars, "Sustainable Scale Up" and "Pioneering Pathways").

Metabolic engineering truly is the ultimate demonstration of continuous manufacturing and is well on its way to evolving into a very handy tool for drug discovery. These developments are the stuff of Drexler's wildest dreams. Perhaps now he might reconsider his stance regarding biology.

Vikramaditya G. Yadav is assistant professor at the Department of Chemical and Biological Engineering, The University of British Columbia, Vancouver, Canada.

Visit our website for more on metabolic engineering, including primers on metabolic pathways and flux, and common techniques. tmm.txp.to/0115/yadav-primers

References:

1. *G. L. Challis and J. H. Naismith, Curr. Opin. Struct. Biol. 14, 748–756 (2004).*
2. *K. E. Drexler, Wiley, New York, NY (1992).*
3. *K. E. Drexler, The Guardian, http://bit.ly/1ohlk8i (14 October 2013).*
4. *K. E. Drexler, The Guardian, http://bit.ly/1eblzqw (21 October 2013).*
5. *R. E. Smalley, Scientific American 285 (3), 76–77 (2001).*
6. *K. E. Drexler et al., Institute For Molecular Manufacturing, http://bit.ly/1t3w80j (2001).*
7. *P. P. Dennis and H. Bremer, J. Molec. Biol. 84, 407–422 (1974).*
8. *R. Baum, Chemical & Engineering News 81 (48), 37–42 (2003).*
9. *S. Mann, Nature 365, 499–505 (1993).*
10. *G. Stephanopoulos, Metab. Eng. 1 (1), 1–11 (1999).*
11. *L. P. Wackett and C. D. Hershberger, American Society Microbiology, Washington, DC (2001).*
12. *M. T. Reetz, J. Am. Chem. Soc., 135 (34), 12480–12496 (2013).*
13. *U. T. Bornscheuer et al., Nature, 485, 185–194 (2012).*
14. *C. Khosla and J. D. Keasling, Nat. Rev. Drug Discov. 2 (12), 1019–1025 (2003).*
15. *V. G. Yadav et al., Metab. Eng. 14 (3), 233–241 (2012).*
16. *R. A. Sheldon, Green Chem. 9, 1273–1283 (2007).*
17. *D. Weiss, P. Naik and R. Weiss, Nat. Rev. Drug Discov. 8, 533–534 (2009).*
18. *K. Plumb, Chem. Eng. Res. Des. 83 (A6), 730–738 (2005).*
19. *G. S. Calabrese, S. Pissavini, Alche J. 57 (4), 828–834 (2011).*
20. *G. Malhotra, Pharm. Processing 27 (8), 16–20 (2010).*
21. *V. G. Yadav, Ind. Eng. Chem. Res., 53 (49), 18597–18610 (2014).*
22. *S. Y. Rojahn, MIT Technology Review, http://bit.ly/1keso2b (10 May 2012).*
23. *D. M. Roberge et al., Chem. Eng. Tech. 28 (3), 318–323 (2005).*
24. *Pennemann, H. et al., Org. Process Res. Dev. 8, 422–439 (2004).*
25. *S. M. Rubenstein and R. M. Williams, J. Org. Chem. 60, 7215–7223 (1995).*
26. *V. G. Yadav, Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA (2013).*
27. *A. Jungbauer and J. Peng, Biotechnol. J. 6, 1431–1434 (2011).*
28. *B. M. Trost, Science 254, 1471–1477 (1991).*
29. *R. Firn, Oxford University Press, Oxford, UK (2010).*

The Bioavailability Toolbox

How can we overcome bioavailability challenges in our increasingly complex drug pipeline?

There is no 'one size fits all' solution to overcoming poor solubility and bioavailability, while delivering an oral dosage form preferred by patients, as we discussed in the first article in the series ("Connecting the Dots in Drug Delivery"). Marrying acceptable solubility with long-term stability is a tough challenge that requires an array of increasingly ingenious formulations.

Since the advent of combinatorial chemistry and high-throughput screening in the 1990s, bioavailability challenges have become more and more complex. In response, new formulations and delivery methods have emerged. The result? Scientists now have an arsenal of techniques to choose from. "It used to be that micronization and the particle-forming step were all that you had, but now with the different formulation options, scientists have a much greater chance of improving bioavailability," says David Igo, Director of Product Development and Manufacturing at Catalent Pharma Solutions.

All the patient sees is a simple tablet or capsule – only a pharmaceutical scientist knows the years of painstaking work that have gone into creating that ideal formulation.

Here, we take a whistle-stop tour of the technology and techniques that enable progress in formulation, focusing on the latest and greatest advances.

Amorphous APIs

Early in the drug development process, a process of solid-state optimization can increase the solubility of the native active pharmaceutical ingredient (API), a much less expensive option than developing complex formulations later on. The 'go to' method for acidic or basic compounds is to identify a suitable crystalline salt of the API, but for some of today's candidate drugs even this option is not straightforward. "Molecules are getting progressively bigger and more complex, and this complexity means that salt formation is sometimes not sufficient to achieve a meaningful improvement in solubility," explains Igo.

An approach that has grown rapidly in popularity over the past decade is the creation of an amorphous solid dispersion. With no crystal structure to break down, amorphous compounds are much more easily dissolved in the GI tract, exhibiting 10,000-fold increases in apparent solubility (1). Amorphous solutions are formed by combining the API with a suitable polymer, by spray drying, hot melt extrusion or co-precipitation, depending on the melting point and how easily they can be dissolved in common organic solvents.

The downside of amorphous formulations is that the physical form of the compound is generally less thermodynamically stable than a crystalline form. This can result in a shorter shelf-life due to the potential of the drug to revert to a crystalline form over time. However, recrystallization can be prevented by understanding and carefully managing the product storage condition relative to the glass-transition temperature or selection of the polymeric carrier, incorporating stabilizers into the polymer or controlling pH (2).

Super dry

Spray drying has been the most widely used method to date, with the API–polymer mix dissolved in an organic solvent, atomized and then rapidly dried with hot air or nitrogen into a fine powder. Spray drying has allowed commercialization of many drugs that would otherwise have failed, says Filipe Gaspar, Vice President of R&D at Hovione. "It is an enabling technology and we have worked on many products that only became bioavailable by adopting it and in many others that became effective drugs at much reduced dose."

So what's next for spray drying? There has been a lot of progress in process analytical technology, according to Gaspar, which allows continuous monitoring of critical quality attributes such as particle size or solvent content. Other areas of innovation include advanced modeling of the process, which provides for seamless scale-up and process optimization with minimum testing, optimization in the capture of the powders and more efficient

operation and cleaning of the units. Considering the comparatively gentle nature of the process and recent advances in sterilization of spray dryers, Márcio Temtem (group leader, Particle Design & Pharmaceutical Development at Hovione) believes the next logical step will be to apply the technique in the manufacture of sterile biopharmaceuticals, in place of freeze-drying: "The technology has significant advantages over lyophilization in terms of cost and throughput. I would say it is just a question of time before its use becomes widespread."

Hot topics in hot melt extrusion

Hot melt extrusion has been underutilized by the pharmaceutical industry, according to Michael Repka, Chair and Professor at The University of Mississippi. "Even though hot melt extrusion has been in use for years, many pharma companies have not fully accepted it. They have been making tablets the same way for 40 years and can be reluctant to replace older technology."

But for APIs with the right properties, the use of hot melt extrusion is rapidly gaining popularity. As the process relies on heat and shear stress to effect molecular mixing and create an amorphous dispersion, there is no need for toxic organic solvents – or the expense and environmental hazard of removing them.

Repka's lab experiments with a variety of different APIs, polymers, temperatures and dosage forms to find the optimum process and to troubleshoot problems, such as recrystallization or high melting point drugs. "Ultimately, our research aims to make hot melt extrusion more efficient and ideally develop platform technologies, so we don't have to start from scratch for every new chemical entity," says Repka.

Recently, the group was successful in using hot melt extrusion alongside high-pressure homogenization to produce solid lipid nanoparticles in a continuous process (3). Repka believes that capitalizing on the inherent continuous processing capabilities of hot melt extrusion will be crucial, as the industry (tentatively) moves towards continuous manufacturing: "If you can develop a continuous rather than batch process, that saves a tremendous amount of time and money and personnel, which means that we can get the product to the patient faster."

"It won't come overnight", says Repka, "but as the equipment becomes better and better, and our understanding of the process grows, more and more pharma companies will come to accept hot melt extrusion as a mainstay."

Size matters

For a crystalline drug, one way to increase solubility during formulation is to reduce the particle size (increasing the surface to volume ratio increases the rate of dissolution in the gastrointestinal tract). It's now possible to reliably produce even the smallest particle sizes in either a 'top down' (for example, milling or micronization) or 'bottom up' (for example, precipitation) fashion. Micronization is the most common approach, with companies offering ever-faster and more efficient milling techniques.

As well as increasing the surface to volume ratio, nanoparticles have intrinsic properties that can help overcome poor bioavailability. The transition from micro- to nano-scale dramatically changes the physicochemical properties of the particles, increasing saturation solubility, speed of dissolution, and the ability of the particles to adhere to cell membranes (4).

Plus, there are special advantages when it comes to targeting cancer. Ronak Savla, a Rutgers University Research Fellow supporting the Catalent Applied Drug Delivery Institute, used specially engineered nanoparticles to deliver highly potent cancer drugs specifically to the tumor site (5). "There is a phenomenon known as the enhanced permeation and retention effect in solid tumors – the blood vessels in the tumor become leaky, allowing the nanoparticles to exit the blood stream only at the tumor site rather than elsewhere in the body."

Savla also applied cutting edge techniques to create nanoparticles for pulmonary (inhaled) delivery (6). Particle

size is key for inhaled formulations, as Savla explains: "The location where the drug particles deposit is highly dependent on size, so if you want to reach the alveoli, deep in the lungs, you need a smaller particle size, whereas if you want to reach the upper airway or bronchus, you need a larger size." It is likely to be a few years before we see the results of Savla's work in the clinic, but experts agree that nanoparticles are a key drug delivery system for the future.

Fat chance

Lipophilic drugs are often better absorbed when taken alongside a fatty meal, a fact which gives a clue to another formulation approach for highly lipophilic compounds. Self-emulsifying drug delivery systems (SEDDS) are created by dissolving the API in a mixture of oil, surfactants and other excipients, which results in a liquid or paste intermediate that can be encased in a soft gel or hard shell capsule. After ingestion, the coating dissolves and the mixture is released into the aqueous environment of the gastrointestinal tract. The excipients added earlier cause the mixture to emulsify in the gastrointestinal tract, forming very small, easily absorbed droplets of dissolved API.

Many poorly soluble drugs also have low permeability. Lipid-based drug delivery systems enhance passive transport through the lipophilic cell membrane and tap into the body's own mechanisms for absorbing fats through the lymphatic system.

New developments in soft gel technology have made it possible for a broad range of drugs to be developed using these techniques. Coated capsules can now delay release of the drug until the capsule reaches the lower intestine – useful for drugs that might cause gastric side effects or where efficacy would be disrupted by the acidic environment of the stomach. In addition, abuse deterrent coatings are available for products like pseudoephedrine, which can otherwise be converted by 'kitchen chemistry' to illegal methamphetamine

Where a solid dosage form is preferred, solid SEDDS have been developed, using solidification techniques, such as spray drying, to convert the liquid intermediate into a standard solid oral dosage form (7).

Winning combinations

Naturally, these approaches do not operate in isolation – they are all part of the wider drug delivery toolkit, where advances in one area often trigger exciting new developments in others. For example, amorphous drug nanoparticles have shown a lot of promise, combining as they do the high solubility of the amorphous state with the rapid dissolution of nanoparticles (8). In a similar vein, the use of nanoemulsions has previously been limited by issues of palatability and formulation, but in combination with self-emulsification and soft gel technologies, nano-SEDDS are now a hot area for research (9).

Ralph Lipp, founding advisory board member of Catalent's Applied Drug Delivery Institute, believes collaboration is key to addressing bioavailability challenges. "It is very important that there is good communication between the drug design and formulation teams within an organization. We need a team approach; a more holistic way of developing drugs," he says.

Collaboration is central to the mission of the Catalent Applied Drug Delivery Institute, which brings academic and industrial scientists together to address current drug delivery challenges. David Igo, Michael Repka and Filipe Gaspar have all contributed to the Institute's regular educational symposia and you can find out more about the next two events in "Collaborate and Innovate".

Despite the range of options now available, scientists can't rest on their laurels – they must work continuously to improve and refine current technologies – and come up with new ones. Gaspar says, "Today, the vast majority of new drugs are poorly soluble and that is a major challenge, but it also creates opportunities for new technologies to be developed in the industry." So innovation is also essential.

In the next article in the series, we'll be gazing into our (amorphous) crystal ball, to see what disruptive technologies will be shaking up drug delivery in the years to come.

References

1. *C. Brough, and R.O. Williams 3rd, "Amorphous Solid Dispersions And Nano-Crystal Technologies For Poorly Water-Soluble Drug Delivery", Int J Pharm. 453(1), 157–166 (2013).*
2. *Y. Huanga and W-G Daib, "Fundamental Aspects Of Solid Dispersion Technology For Poorly Soluble Drugs", Acta. Pharm. Sinica B 4(1), 18–25 (2014).*
3. *H. Patil et al., "Continuous Manufacturing Of Solid Lipid Nanoparticles By Hot Melt Extrusion", Int. J. Pharm. 471(1-2), 153–156 (2014)*
4. *S. M. Alshahrani et al., "Stability-enhanced Hot-melt Extruded Amorphous Solid Dispersions via Combinations of Soluplus® and HPMCAS-HF", AAPS PharmSciTech (January 2015).*
5. *R. Savla et al., "Tumor-Targeted Responsive Nanoparticle-Based Systems For Magnetic Resonance Imaging And Therapy", Pharm. Res. 31(12), 3487–3502 (2014).*
6. *R. Savla and T. Minko, "Nanotechnology Approaches For Inhalation Treatment Of Fibrosis", J Drug Target. 21(10), 914–925 (2013).*
7. *Tan, S. Rao and C. A. Prestidge, "Transforming Lipid-Based Oral Drug Delivery Systems Into Solid Dosage Forms: An Overview Of Solid Carriers, Physicochemical Properties, And Biopharmaceutical Performance", Pharm. Res. 30(12), 2993–3017 (2013)*
8. *W. S. Cheow et al., "Amorphization Strategy Affects the Stability and Supersaturation Profile of Amorphous Drug Nanoparticles", Mol. Pharmaceutics 11(5), 1611–1620 (2014).*
9. *A. A. Date et al., "Self-Nanoemulsifying Drug Delivery Systems: Formulation Insights, Applications And Advances", Nanomedicine (Lond). 5(10), 1595–1616 (2010).*

Best Practice

Technology
Quality
Compliance

34-36
How to Embed Excellence
You've decided to implement an operational improvement program in your facility. But where do you start, and how do you measure progress?

How to Embed Excellence

Having witnessed the evolution of operational excellence (OPEX), how do you implement it – and how do you ensure continued success? Here, we propose a new model.

By Thomas Friedli, Christian Mänder and Nicolas Ponce

In our previous article in The Medicine Maker (1), we traced the evolution of Operational Excellence (OPEX), from increasing regulatory pressure in the early 2000s for more transparent manufacturing processes, to today's widespread adoption of OPEX principles. Most pharmaceutical plants in both Europe and the US have been running operational improvement programs for years. But the journey to excellence is a never-ending one if you want to maintain success.

In 2014, with our St. Gallen OPEX benchmarking project in its tenth year and 277 data sets in our database (2), we felt the time was right to further develop our ideas around the future of OPEX. In particular, we wanted to align our research with the current needs of the industry. With this in mind, we launched a new global research collaboration with four of the world's biggest pharmaceutical companies. We held a series of meetings, both on neutral ground and 'amidst the action' at manufacturing sites, to discuss the current challenges of the industry and how OPEX could be better implemented.

Our participants all faced similar challenges and a number of questions kept coming up in workshop discussions. How do we embed an OPEX program over time? How do we maintain a successful OPEX program? And how do we measure progress? These FAQs led us to the idea of an OPEX maturity model that could be used to assess OPEX performance on site. Figure 1 shows the first draft of the model and recommends an order for tackling different aspects. Here, we will introduce the key parts of our model, define the individual maturity stages and explain how the level of maturity of a site is assessed. Let's start by describing each step of OPEX implementation.

Step 1: Equipment Stability

The goal of this first maturity level is to achieve highly stable manufacturing equipment – after all, it is impossible to create robust processes without reliable equipment. A production site can be said to have achieved Equipment Stability when there is a genuine sense of urgency to maximize equipment effectiveness and improve maintenance efficiency. As equipment breakdowns can lead to production downtime and bring about a crisis, the concept of total productive maintenance, in which all workers learn how to clean, inspect and maintain equipment, is something that we believe is crucial in the quest for an excellent production environment.

Step 2: Process Stability

Process Stability is achieved when a manufacturing plant has internalized the principles of total quality management, which involves continuously isolating variables that cause deviation, mastering them and, by doing so, steadily improving their processes in the direction of flow. A special emphasis on variance

minimization leads to a more stable and better-controlled manufacturing process, which in turn reduces the need for safety stock to act as a buffer. Moreover, the plant ensures that supplier quality management is up to the same standard by integrating suppliers into the internal quality system.

Step 3: Low Inventories

The third step is to reduce operating inventory to increase flexibility and responsiveness. Following the just-in-time (JIT) principle, the site produces what is needed on receipt of a signal from the customer. With the goal of one-piece flow (continuous manufacturing) and minimal buffer inventory, it's obvious that this maturity level requires stable equipment and robust processes; therefore, the first two levels must have been mastered first, if you don't want the danger of the whole underlying system starting to crash.

Step 4: Continuous Improvement

Step 4 is the end goal but also a moving target given its name. It is the stage at which we can truly say that we have achieved OPEX. It is reached when all the requirements of each maturity level have been met, with appropriate practices put in place. However, the journey should continue with a commitment to ongoing efforts to stay competitive by improving products, services and processes, and by collaborating with suppliers and customers to share the benefits.

Assessing Progress

For each maturity level there is a set of requirements that have to be met, and achieving these means applying a variety of practices. Measures put in place by the site leadership team don't need to be complex and in many cases a single process or program may fulfil the intent of one or more requirements. For example, simple housekeeping activities like maintaining a checklist to continuously monitor the condition and cleanliness of the machines and equipment has a high impact on equipment stability but also on the overall quality management of the plant. On the other hand, sometimes meeting a single requirement may

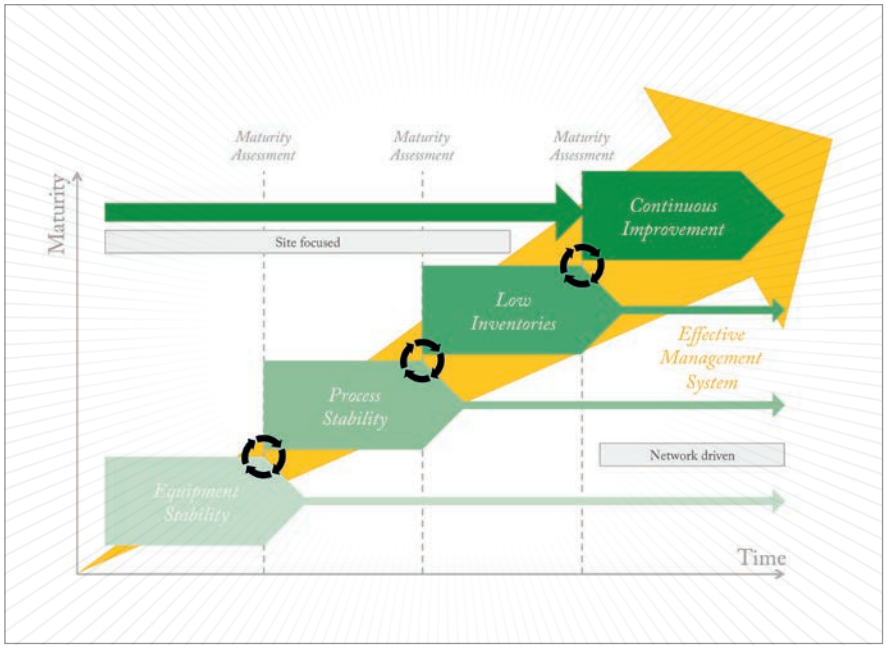


Figure 1: The St. Gallen Operational Excellence Maturity Model. A suggested order for implementing the different stages of OPEX and assessing performance.

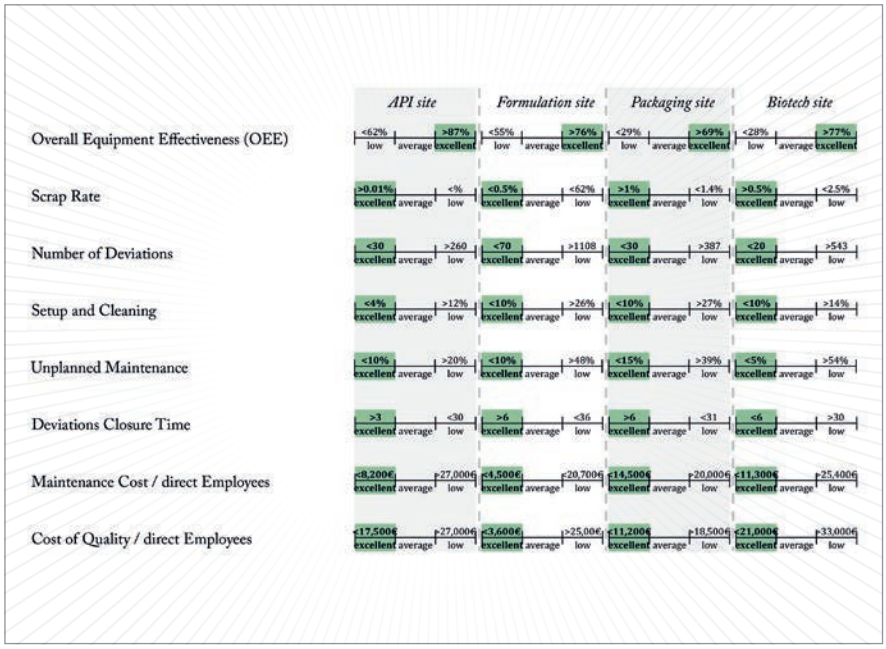


Figure 2: Low, average and excellent performers in the individual performance categories.

Stability Enablers

Companies who agree with the following statements are more likely to achieve stability.

- In our company direct and indirect processes are well documented.
- We continuously measure the quality of our processes by using process measures (e.g., on-time-in-full delivery rate).
- Our process measures are directly linked to our plant objectives.
- In our company there are dedicated process owners who are responsible for planning, management and improvement of their processes.
- A large percentage of equipment on the shop floor is currently under statistical process control (SPC).
- We make use of statistical process control to reduce variances in processes.
- For root cause analysis we have standardized tools to get a deeper understanding of the influencing factors.

These factors had a statistically significant impact on the following KPIs

- Changeover time
- Production schedule accuracy
- Unplanned maintenance

take multiple efforts. For example, to achieve a high level of equipment effectiveness, there are several activities that have to be put in place by the site leadership team, including deploying a formal program for maintaining the machines and equipment, identifying all potential bottleneck machines and supplying additional spare parts, as well as emphasizing good maintenance as a strategy for increasing quality and planning for compliance. Strong management commitment will also be required to provide support in the form of playbooks, methodologies, coaching, and training and certification of staff.

Maturity level assessments should be conducted to validate site performance and are an effective and consistent way of measuring a site's progress along the pathway to OPEX. The assessments, developed by the University of St. Gallen, are designed to allow production sites to verify whether they have reached the next maturity level. The assessment, which is carried out by the companies in collaboration with the University, occurs when the site leadership team believes the site has completed the requirements for the next level. The scope of the maturity level assessment includes:

- verification of performance results
- verification of required practices
- review of the diagnostic process and action plans

The assessments should be as frank and open as possible to avoid misunderstandings and misleading implications. The best approach is to use multiple assessments by different people from different departments. One person should consolidate the findings and be responsible for feedback and follow up to ensure the quality of the data.

If the site meets the requirements for the next maturity level, the actions are submitted as shared practices for the entire network as one of the outputs from the maturity level assessment. The output form of a (failed) maturity level assessment includes an action plan to fulfill any requirements that have not been met (including root cause analysis).

The basic ideas we developed and discussed in our workshops were also backed up with data from the St. Gallen OPEX database, which allowed us to analyze the correlation between excellent performance in the chosen key performance indicators (KPIs) and specific enabling factors. Figure 2 shows how we define excellence in a range of KPIs. The numbers in Figure 2 are based on the St. Gallen OPEX database. The excellence scores were derived by using the top ten percent of the included sites, while the low performance scores relate to the bottom ten percent of the sites that participated in the St. Gallen OPEX Benchmarking. "Stability Enablers" shows the enablers that support strong performance in the individual categories. The results of the statistical analyses show that companies who implement these measures have higher performance - they are the key to achieve a superior maturity level.

We hope that our Maturity Model will help you to measure your OPEX success and ultimately help drive the industry as a whole on its never-ending journey to excellence. Working with industry and conducting the workshops was incredibly valuable for us and we plan to continue this exchange platform in 2015 to ensure that the future of OPEX remains bright.

Thomas Friedli is Associate Professor of Management, and Christian Mänder and Nicolas Ponce are Research Associates, at the University of St Gallen Institute of Technology Management.

References

1. *T. Friedli, C. Mänder and P. Basu, "The Evolution of Operational Excellence", The Medicine Maker 2, 30 (2014).*
2. *T. Friedli et al., "Leading Pharmaceutical Operational Excellence", Springer Verlag, Berlin (2013).*
3. *T. Friedli et al., "Operational Excellence in the Pharmaceutical Industry", Editio Cantor Verlag, Aulendorf, Germany (2006)*

Ingredients | Finished formulation | BioPharma | Technology | Packaging | Excipients | Custom manufacturing | Natural extracts | Fine chemicals | Intermediates | General

Reach the ASEAN pharma market

01 Indonesia is projected to be the fastest-growing economy within the ASEAN, with an average annual growth rate of 6% in 2014-2018.

02 The potential of Indonesia's pharmaceutical market is boosted by government's aim to provide universal health coverage in 2014. Healthcare spending in Indonesia is projected to reach US$21.7 bn in 2015.

03 The government economic plan aims to increase GDP per capita from US $3,000 to US $15,000 by 2025[1]

04 CPhI South East Asia, co-located with P-MEC South East Asia and InnoPack is the right platform, where you can meet ASEAN decision makers and business partners within the pharmaceutical industry with a potential of US$80 billion pharmaceutical market value at retail price in 2017.

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

Register as a visitor with media code:

SEA000011FOH

URL: http://www.cphi.com/asean

3 Pharma Events under 1 roof

CPhI south east asia | P-mec | InnoPack

8-10 April 2015 • Jakarta International Expo • Indonesia

"ASEAN's booming pharmaceutical event & conference platform"

Organised By: UBM

the Medicine Maker

Power List

2015

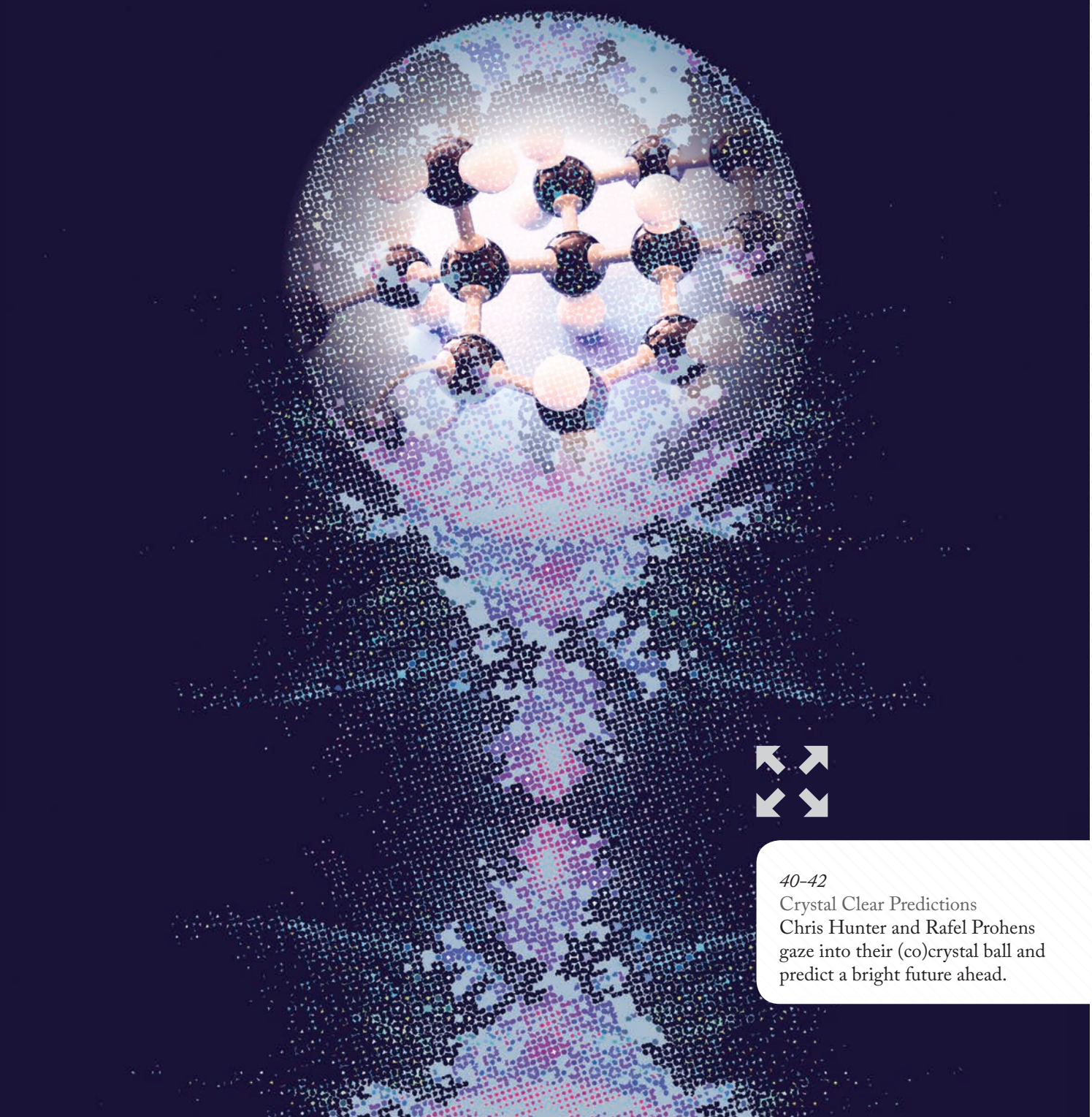
Who are the role models and thought leaders that inspire you?

The Medicine Maker Power List 2015 will rank the top 100 most influential people in drug development and manufacture, as nominated by our readers.

To nominate or find out more,
go to http://tmm.txp.to/2015-powerlist

NextGen

R&D pipeline
New technology
Future trends

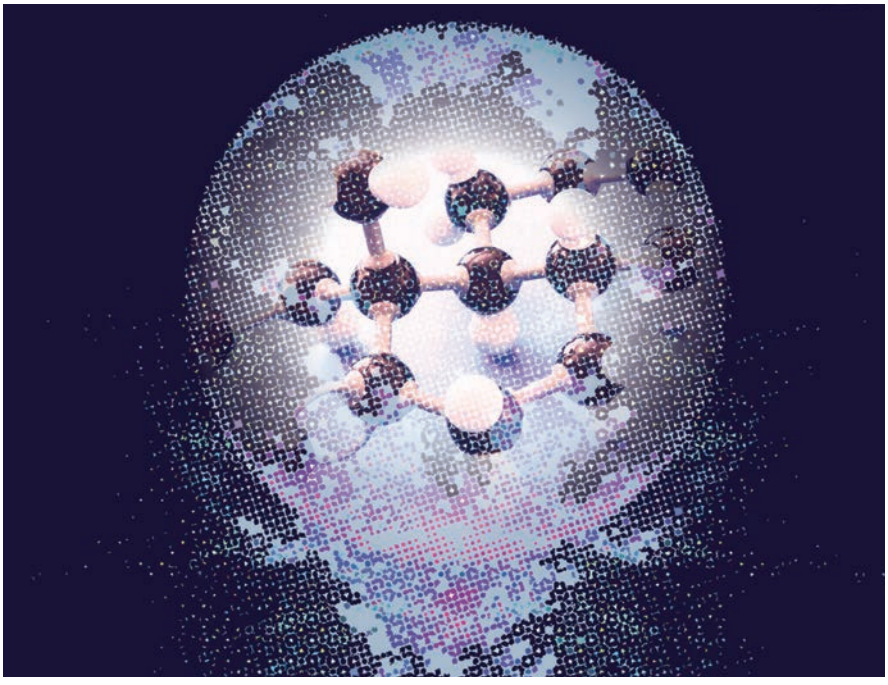


40-42
Crystal Clear Predictions
Chris Hunter and Rafel Prohens gaze into their (co)crystal ball and predict a bright future ahead.

Crystal Clear Predictions

A new model for cocrystal formation could be a powerful tool for formulation scientists – no crystal structures required, it's all about the surface contacts.

By Christopher A. Hunter and Rafel Prohens



Cocrystals – two or more molecular entities combined in a homogenous crystalline structure – have recently become attractive targets for the pharmaceutical industry, as cocrystallization can have a positive effect on the properties of solid dosage forms. However, predicting which potential coformers will successfully cocrystallize with a given active pharmaceutical ingredient (API) has proved difficult. Here, we describe a new computational method that does not require any knowledge or prediction of three-dimensional crystal structures, making it fast enough to virtually screen very large libraries of compounds to successfully identify new API cocrystals.

Hunting cocrystals

Formulation of a drug as a cocrystal can change the bioavailability, dissolution rate, physical and chemical stability, compressibility and hygroscopicity, and new multicomponent solid forms offer the possibility of releasing an API without infringing the originator's patent (1). Cocrystals may also occur as multiple polymorphs, suggesting additional options to modify properties, increased patent protection and improved formulations. In 2012, the FDA issued a set of guidelines to regulate the use of pharmaceutical cocrystals and concluded that a cocrystal should be considered as a drug product intermediate and not as a new API (2). In July 2014, the European Medicines Agency (EMA) published a reflection on the use of cocrystals of active substances in medicinal products and determined that cocrystals were eligible for generic applications in the same way as salts (3).

Cocrystals have a number of advantages over salts. For example, there are a large number of potential coformers contained in the GRAS (Generally Regarded as Safe) and EAFUS (Everything Added to Food in the United States) lists published by the FDA. In contrast to salts, the formation of a cocrystal does not rely on ionization, so it is not limited to APIs containing acidic or basic functional groups. This means that the structure space of potential formulations with improved properties is vast. However, this spectacular potential presents the experimental scientist with a difficult challenge: how can we navigate such a vast molecular landscape?

The crystal maze

Historically, a knowledge-based approach has been used to select appropriate cocrystal coformers, exploiting experimental data contained in the Cambridge Crystallographic Database. This approach to structure-based cocrystal design uses a statistical analysis of functional group interactions in the solid state to identify supramolecular synthons. Supramolecular synthons have their origins in the lock and key principle described by Emil Fischer in 1894 (4) and were defined by Gautam Desiraju as "structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions" (5).

In the 1980s, Margaret Etter deduced a set of empirical rules, which many chemists have used to predict the formation of multicomponent crystals (6). While the synthon approach focuses on structure, Etter's rules provide a recipe for predicting which interactions are most likely to occur in the solid state based on energetics. The preliminary

steps in the design of multicomponent crystal phases has traditionally incorporated both strategies, identifying reliable supramolecular synthons and using empirical data to estimate an energetic hierarchy. However, cocrystal prediction is hampered by variations in cocrystal stoichiometry, the presence of secondary weaker intermolecular interactions and the possibility of additional components, such as solvent molecules. Reliable prediction of whether a specific API and coformer will actually cocrystallize remains a challenge, and as a result, cocrystal preparation is still mainly conducted through trial-and-error experimental screening.

Put simply, we expect a cocrystal to form if it is thermodynamically more stable than its components. Thus, understanding the energetics of non-covalent interactions is essential for predicting whether a particular combination will form a cocrystal. In principle, the energetics of cocrystal formation could be calculated directly using ab initio methods (7). However, one of the biggest limitations in the development of computational methods for predicting cocrystal formation is that a crystal structure must be known to calculate the lattice energy. The area of crystal structure prediction is still in its infancy, so we need an alternative approach for practical applications in virtual cocrystal screening.

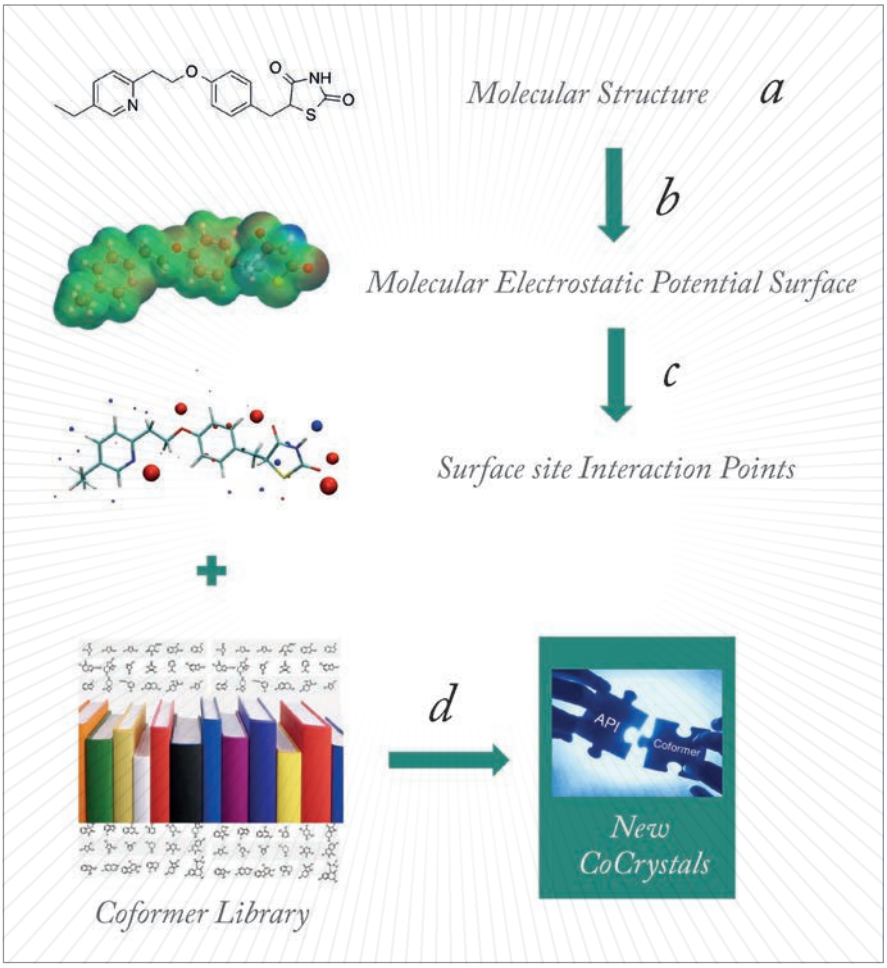


Figure 1. A virtual cocrystal screen. (a) the API is drawn in an extended conformation, (b) quantum chemistry is used to calculate 3D structure and MEPS, (c) the MEPS is converted into SSIPs, (d) the SSIPs are used to calculate the probability of cocrystal formation for each compound in a large library of potential coformers and the most promising candidates are selected for experimental testing.

A new approach

My research group and I (Chris Hunter) at the University of Cambridge have been working for over a decade on a project that uses a surface-based approach to non-covalent chemistry to describe the thermodynamics of intermolecular interactions in solution. The theory was first published in 2004 (8), and the approach has since been validated for H-bonds, halogen-bonds and aromatic interactions, for the effects of solvent and solvent mixtures on solution-phase molecular recognition, and for phase transfer properties like logP (9–12). The great advantage of this approach is that it integrates theoretical ideas and experimental observations about intermolecular interactions in the gas phase, in the solid state, and in solution – all using a single unified framework.

Our approach assumes that the free energies of all intermolecular interactions in the condensed phase can be understood based on the gas phase electrostatic properties of the isolated molecules. Intermolecular interaction free energies are calculated using a set of discrete surface-site interaction points (SSIPs), which are characterized by parameters (α and β) that quantify the properties of positive (usually H-bond donor) and negative (usually H-bond acceptor) sites on the molecular surface. A condensed phase is treated as an ensemble of all possible interactions between collections of SSIPs, without considering three-dimensional structure, which tremendously simplifies the calculation of thermodynamic properties, such as the

probability of cocrystal formation.

The application of this approach to cocrystal formation in the solid state follows the Etter principle that the structure of a crystalline solid is determined by a hierarchical organization of SSIP interactions. Accordingly, the strongest interaction is expected to be formed between the SSIP with the largest α (the best H-bond donor) and the SSIP with the largest β (the best H-bond acceptor), the next strongest interaction will be formed between the SSIP with the next highest α and the SSIP with the next highest β, and so on, until all of the SSIPs are used in the construction of the crystal structure. Summing the energies of these SSIP contacts gives the total non-covalent interaction energy of the solid. This can be done for the pure API, the pure coformer and for cocrystals of any desired stoichiometry, to establish whether the cocrystal is likely to be able to make an energetically more favorable set of non-covalent interactions than the components. This approach provides a very straightforward method for evaluating the probability of cocrystallization.

Energy versus structure

A key feature of our SSIP approach is that three-dimensional structure is not considered, so prediction of the precise arrangement of the molecules is not required to calculate the SSIP pairing energy in a crystalline solid. Since most molecules have on the order of ten near neighbors in a crystal, it is likely that the ten most important intermolecular SSIP contacts can be achieved by some packing arrangement. The top ten SSIP contacts will include all of the energetically most important interactions, and since the energies of all of the weaker interactions are rather similar to one another, whether or not contacts are made in exactly the manner predicted by the Etter hierarchy does not significantly affect the overall energy of the crystal.

Moreover, it is not necessary to distinguish between different possible intermolecular interactions that are similar in energy. For example, if a molecule contains two very strong H-bond donors (D1 and D2) with similar α parameters and two very strong H-bond acceptors (A1 and A2) with similar β parameters, it does not matter whether the SSIPs pair one way, A1 with D1 and A2 with D2, or the other, A1 with D2 and A2 with D1. The overall energy of the crystal will be the same, even though the three-dimensional structures of the crystals will be completely different. This is the origin of polymorphism: different crystal structures with very similar energies. The fact that polymorphs generally differ by a few kJ mol^{-1} in energy demonstrates that structure does not matter as far as the energetics of SSIP contacts go.

The freedom to calculate energy without structure is the key to the speed of the SSIP approach and makes it viable to conduct virtual cocrystal screens on very large compound libraries. The method has now been experimentally validated for several different APIs and we believe it represents a powerful new tool in the armory of the solid-state formulation chemist (13-15).

Christopher A. Hunter FRS is the Herchel Smith Professor of Organic Chemistry at the University of Cambridge, UK, and Rafel Prohens is Scientific Director and co-founder at CIRCE Crystal Engineering and manager of the Polymorphism and Calorimetry Platform at the University of Barcelona.

References

1. *N. Blagden et al., "Crystal Engineering of Active Pharmaceutical Ingredients to Improve Solubility and Dissolution Rates", Advanced Drug Delivery Reviews 59, 617–630 (2007).*
2. *Food and Drug Administration, "Guidance for Industry: Regulatory Classification of Pharmaceutical Co-Crystals", www.fda.gov (2013).*
3. *European Medicine Agency, "Reflection Paper on the Use of Cocrystals and Other Solid State Forms of Active Substances in Medicinal Products", www.ema.europa.eu (2014).*
4. *E. Fischer, "Einfluss der Configuration auf die Wirkung der Enzyme", Ber. Dtsch. Chem. Ges. 27, 2985 (1894).*
5. *G. R. Desiraju, "Supramolecular Synthons in Crystal Engineering—A New Organic Synthesis", Angew. Chem. Int. Ed. 34, 2311 (1995).*
6. *M. C. Etter, "Encoding and Decoding Hydrogen-Bond Patterns of Organic Compounds", Acc. Chem. Res. 23 (4), 120–126 (1990).*
7. *S. L. Price, "Predicting Crystal Structures of Organic Compounds", Chem. Soc. Rev. 43, 2098–2111 (2014).*
8. *C. A. Hunter, "Quantifying Intermolecular Interactions: Guidelines for the Molecular Recognition Toolbox", Angew. Chem. Int. Ed. 43, 5310 (2004).*
9. *C. S. Calero et al., "Footprinting Molecular Electrostatic Potential Surfaces for Calculation Of Solvation Energies", Phys. Chem. Chem. Phys 15, 18262–18273 (2013).*
10. *C. A. Hunter, "A Surface Site Interaction Model for the Properties of Liquids at Equilibrium", Chem. Sci. 4, 1687–1700 (2013).*
11. *S. L. Cockroft and C. A. Hunter, "Resolvation and Substituent Effects in Edge-To-Face Aromatic Interactions", Chem. Commun. 3961-3963 (2009).*
12. *R. Cabot and C. A. Hunter, "Non-Covalent Interactions Between Iodo-Perfluorocarbons and Hydrogen Bond Acceptors", Chem. Commun. 2005–2007 (2009).*
13. *D. Musumeci et al., "Virtual Cocrystal Screening", Chem. Sci. 2, 883–890 (2011).*
14. *T. Grecu et al., "Validation of a Computational Cocrystal Prediction Tool: Comparison of Virtual and Experimental Cocrystal Screening Results", Cryst. Growth Des. 14, 165–171 (2014).*
15. *T. Grecu et al., "Virtual Screening Identifies New Cocrystals of Nalidixic Acid", Cryst. Growth Des., 14, 1749–1755 (2014).*

INTRODUCING OUR NEW PHARMACEUTICAL COMPENDIUM SERIES

HEAR FROM INDUSTRY EXPERTS

View our latest webinars - from users meetings talks, posters & oral presentations - all in one place.

VIEW OUR COMPENDIUM SERIES

Our comprehensive collection of articles on peptide and protein bioanalysis addresses several challenges faced by bioanalytical scientists in today's complicated world of large molecule bioanalysis.

NEED TRAINING?

Access comprehensive instrument and application based training courses, which cover a wide range of workflows, methods and compounds.

Email **pharmaceutical@absciex.com** to register today and be kept up to date with our latest releases

AB SCIEX

Inform, Innovate and Connect

FLASH PRICE £999 T&C apply

11TH ANNUAL

BioProcess™ INTERNATIONAL EUROPEAN SUMMIT

Tuesday 14 - Wednesday 15 April 2015 • Swissôtel Düsseldorf Neuss, Germany

Where industry connects to share new ideas and innovations across all phases of bioprocess development

Keynote Speakers

Managing Quality across Manufacturing Networks
Dr Anthony Mire-Sluis, Amgen

Low Cost, High Volume Manufacturing
Dr Rahul Singhvi, Takeda Vaccines

Supporting the FDA's "Breakthrough Designation"
Dr Niklas Engler, Roche

Flexible CMC and Continuous Processing
Dr Jens Vogel, Boehringer Ingelheim

Future Manufacturing Technologies
Dr Roman Necina, Baxter

Driving out Inefficiencies
Dr Craig Smith, Thermo Fisher

Future of Biomedicines
Dr Günter Jagschies, GE Healthcare

- Conference 1: ADCs, Novel Therapies and Biosimilars
- Conference 2: Cell Culture, Upstream Processing and Process Analytics
- Conference 3: Downstream Processing and Continuous Manufacturing
- Conference 4: Manufacturing, Single-Use and Quality Management
- Conference 5: Analytics, Quality Control and Formulation

Corporate Sponsors

GE Healthcare Life Sciences

novasep

life technologies | Thermo SCIENTIFIC

Associate Sponsors

RepliGen

BD

www.bpi-eu.com

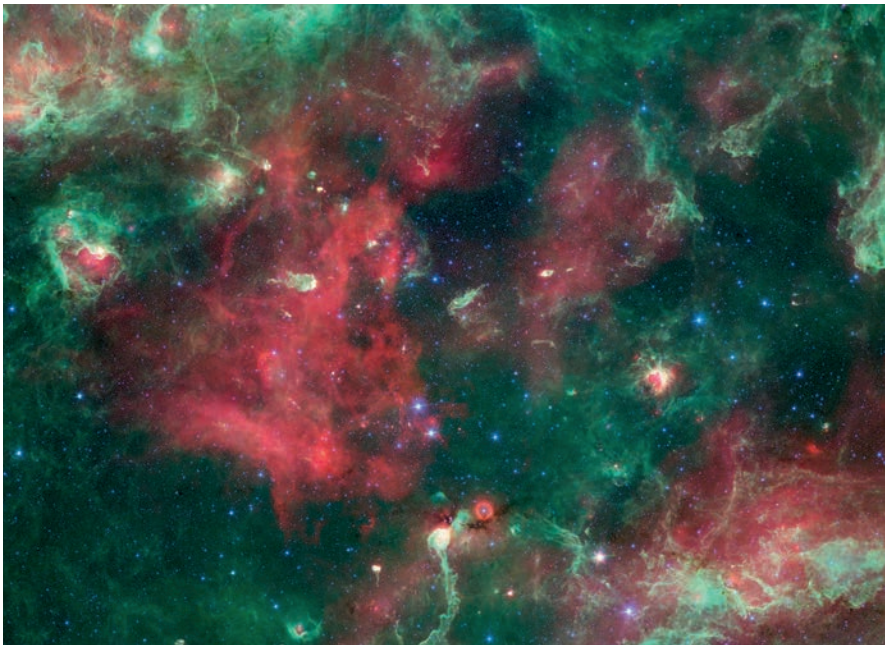
To register: +44 (0) 20 7017 7481
registrations@informa-ls.com

Please quote:
CQ3532MM

Profession

Your career
Your business
Your life

46–48
To Boldly Go...
Pharma must rediscover its innovative spirit, says Duncan Emerton.



Rediscovering Innovation

If pharma is to retain its reputation as an innovator, companies must be brave enough to explore new areas, new targets and new technologies – and boldly go where no industry has gone before.

By Duncan Emerton

First question: is there an innovation drought in pharma? Well, it really depends on what you read and whom you believe.

In 2010, the Boston Consulting Group analyzed R&D productivity and found that the number of new molecular entities (NMEs), including biologics and small molecules, brought to market by per billion dollars of R&D expenditure had fallen by a factor of 100 in inflation-adjusted terms between 1950 and 2010 (1). Then in 2011, the Frankel Group published a white paper on the current state of R&D in the pharma industry and concluded "an innovation drought currently exists in the pharmaceutical industry that is significantly affecting the cash flow of the current business model"(2). Two eminent organizations, pretty much the same conclusion. Pharma R&D is in a mess...

I admit, these papers were written in 2010 and 2011, and here we are in 2014; things must have improved, surely? Perhaps they have. At the end of 2013, the European Medicines Agency (EMA) approved 38 NMEs, compared to 35 in 2012 (3). Between 2010 and 2012, NME output also rose at the FDA. At the end of 2012, the FDA had approved 39 NMEs, up from 30 in 2011. Aside from a dip in the number of NMEs approved by the FDA in 2013, to 27 (4), recent figures suggest the innovation drought is coming to an end. By mid-December 2014 the FDA had approved 35 NMEs (5), so it seems innovation is making a long-waited return to pharma. Or is it?

I've spoken to several experts on the topic who believe that much of what pharma companies are doing today is defensive and reactionary – responding to ever-decreasing returns on investment, shortening product lifecycles and limited long-term thinking. With incremental innovation and short-term profit being prioritized ahead of true innovation and longer-term benefits to society, many believe that things need to change (6).

Defining innovation

Innovation within today's pharma industry exists across a continuum (Figure 1). At one end of the continuum innovation focuses on developing drugs about which relatively little is known at the time of their discovery. These are hailed as the game-changers; the products that have changed treatment paradigms and delivered significant improvements in human health (monoclonal antibodies are a good example). In many ways, they are hailed as 'revolutionary'.

At the other end, innovation focuses on 'tweaking' and 'tinkering' with products that companies already know a lot about. Even minor changes to current products have the potential to deliver strong patient benefits and represent an 'evolutionary' approach to innovation (for example, child-friendly formulations).

The cost and impact of each type of innovation can vary hugely, and can be influenced by the class of product (small molecules or biologic), geography (developed or emerging markets), internal capabilities (vertically integrated or reliant on external partners), therapy area (chronic or acute), and specific indication (adult or pediatric forms of a disease). Suffice to say, making decisions about which type of innovation a company wants to invest in, whether it be evolutionary or revolutionary, or both, isn't simply about flipping a coin.

Driving innovation

There are many key drivers (and a number of resistors) of innovation within the pharma industry. These include internal company issues such as company size, level of R&D investment, therapy area focus and partnering strategy, and external market issues like the regulatory environment, government policy, levels of competition and unmet needs. Despite the complexity of variables, the experts I've spoken to keep coming back to the same three key areas time and time again – policy, partnerships and strategy.

Red tape or green light?

Government support of pro-innovation

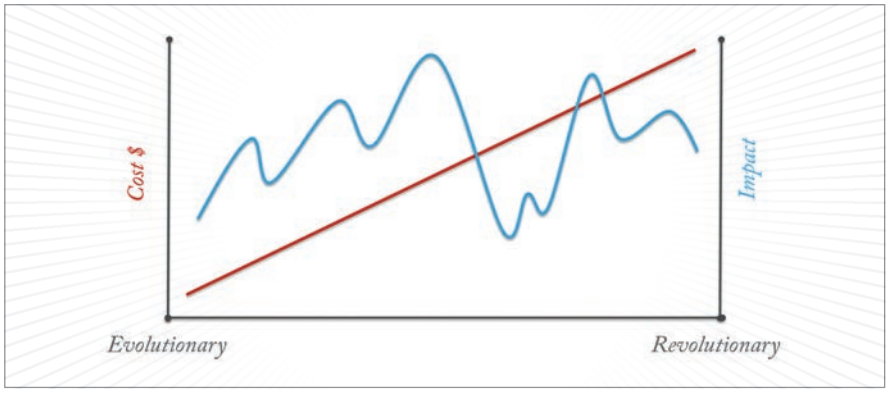


Figure 1. Mapping innovation across a continuum. Costs rise as companies engage in revolutionary, rather than evolutionary, innovation but the impact is difficult to predict.

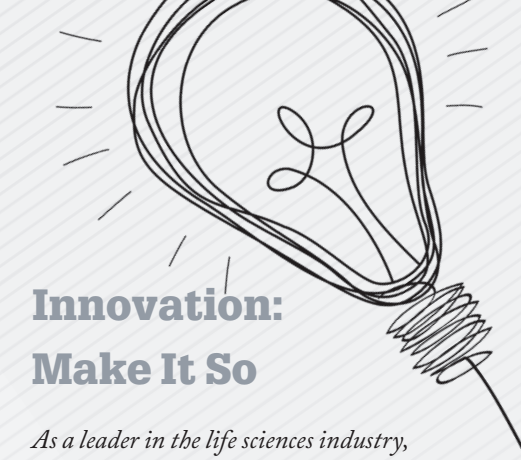
policy remains a critical driver. The Organization for Economic Co-operation and Development argued back in 2006 that there was "…an inability at the national level to address various issues that could promote innovation within the biopharma industry," and recommended a focus on several key areas, including more effective public governance systems, the promotion of co-operation, and networking (7). Progress is being made, for example, orphan disease R&D policies in the US and Europe, and Europe's Innovative Medicines Initiative. In terms of regulation, one could argue that a heightened sensitivity amongst regulatory agencies has contributed to a slowdown in innovation within the biopharma industry. Some high-profile product withdrawals have made the process of passing regulatory muster more and more difficult in recent years. An opposing view is that a rigorous regulatory system actually stimulates innovation. In a seminal analysis of regulation and innovation published in 1978, Grabowski et al. argued that "…more demanding regulatory apparatus, such as the US and UK, has fostered a more innovative and competitive pharmaceutical industry" (8).

Networks and partnerships

As the search for innovation becomes more expensive, time consuming and regulated, pharma companies have adopted strategies that leverage external expertise and collaborative approaches to meet the challenge. 'Collaborative innovation' is becoming the new norm in pharma R&D as companies seek to accelerate and refine the R&D process. Several partnerships have emerged in recent years between pharma and academic institutions (9), insurance companies (10), and non-profit research alliances (11). Perhaps the most high-profile example of pharma collaboration came in February 2014 when ten companies joined forces with the US National Institutes of Health to discover new medicines for diseases such as Alzheimer's, type 2 diabetes, rheumatoid arthritis and lupus (12). More partnerships of this nature can be expected, but only if they deliver value to society.

Small is beautiful

In pharma R&D, surely bigger is better? More cash to invest in R&D, more pipeline assets, more chance of developing something truly innovative? Apparently not. An analysis of the NME output of large pharma companies has shown that being bigger does not guarantee success. In fact, the opposite seems to be true. Since the early 1980s, big pharma's share of NMEs approved has been declining, whereas the small biopharma and biotech companies' share has been increasing (13). Mergers and acquisitions (M&A) don't seem to be solving the issue either. In fact, M&A in the pharma industry have been blamed for having a "negative impact on innovative performance" (14). A leading expert on the subject of innovation in pharma once told me that for large companies, M&A does not seem to create or destroy value, rather, the impact of M&A in the pharma industry on R&D can be viewed as 1+1=1. Regardless of the size and strategy of a company, innovation must be sustainable, allowing the company to thrive in the



Innovation: Make It So

As a leader in the life sciences industry, how can you make sure you are encouraging innovation?

1. Be clear what innovation means to you as a business, what value you can deliver, and go for it!
2. Know where your organization sits on the innovation spectrum; if you're not happy where you are, make changes to move!
3. Make sure everyone in the business understands what's needed to drive innovation; if people don't understand, provide information that clearly establishes the company's innovation strategy and what people can do to support it.
4. Do not be scared of asking the hard questions of senior management to make sure you're in good "innovation health."
5. Be clear on the critical success factors that your organization must focus on in order to maximize your chances of success.

current market environment. There are several viable strategies:

- Focusing on one therapy area (Novo Nordisk).
- Selling products and services in addition to drugs (Bausch & Lomb).
- Becoming embedded in a specific country.
- Diversifying into certain adjacencies (for example, animal health, consumer health).
- Concentrating on generics.

For some companies, the best results may come from a blend of such strategies.

Delivering innovation

How can we reverse the innovation drought? Pharma companies must understand that they are part of a diverse, complex 'innovation ecosystem' that relies on symbiotic relationships to thrive. Notwithstanding this, pharma companies do have one of the more important roles – they spend money on R&D, shoulder most of the risk and must continue to move outside of their comfort zone, if real progress is to be made. However, without enlightened policy makers and contributions from physicians, payers, patients and other important groups, innovation will stall. Like a fine Swiss watch, each component of the innovation ecosystem is indispensable.

The innovation 'audit'

Albert Einstein once said that insanity is defined as "doing the same thing over and over again and expecting different results." Therefore, it is important that companies regularly audit themselves to assess and track their 'innovation health', very simply defined as how innovation is nurtured within the organization, including planning, investment, long-term strategy and making sure the organization learns from its mistakes and failures. If nothing else, it will prevent companies from making the same mistakes again and again, and curb wastage of precious time and resources. If you are charged with driving a company's R&D strategy forward you must not shy away from asking difficult questions of management if the company's strategy is not clear or well defined. Equally, those of you in management must ensure that all key stakeholders within the organization understand the strategy, provide open channels of communication to discuss and resolve issues quickly, and give employees the necessary tools and resources they need. Fundamentally, a company must be comfortable with the decisions it makes about what type of innovation to invest in (revolutionary versus evolutionary), and be prepared to change direction and focus if required.

An innovation-rich future?

Despite concerns over declining output and R&D effectiveness, several experts and key industry stakeholders believe that the pharma industry is about to enter a golden era of innovation. The mistakes of the past, they hope, have been learned and a new generation of pharma industry leaders is now developing new models of innovation in an attempt to deliver growth, shareholder value, and something meaningful for society. The industry must not become complacent, however. Companies must be brave by exploring new areas, new targets and new technologies. Companies must also seek to strike the optimal balance between collaboration and competition; while innovation is driven by competition, even a big pharma company can't do everything internally. And perhaps most critically, companies need visionary leadership (see "Innovation: Make It So"). As a leader you must trust your workforce, empowering them to make bold decisions about the future of your business, and giving them sufficient time and resources to take longer-term risks on what could be the next medical revolution.

References

1. *Boston Consulting Group, "Life Sciences R&D: Changing the Innovation Equation in India", www.bcg.com (September 2010).*
2. *B. Frankel et al., "The Current State of Pharmaceutical Industry Research and Development", www.frankelgroup.com (December 2011).*
3. *EMA Press Release, "EMA Recommends 81 Medicines for Marketing Authorisation in 2013", www.ema.europa.org (January 2014).*
4. *B. Munos, "The FDA Approvals of 2013: a Watershed?", Forbes, www.forbes.com (3 January 2014).*
5. *A. Ward, "Signs of a Revival in Drug Development", Financial Times, www.ft.com (10 December 2014). FT,www.ft.com (10 December 2014).*
6. *TCP Innovations, "Drug Prices are (Unnecessarily) High Because R&D is (Unnecessarily) Inefficient", www.tcpinnovations.com (April 2014).*
7. *OECD, "Innovation in Pharmaceutical Biotechnology; a Comparison of National Systems", www.oecd-ilibrary.org (March 2006).*
8. *H. Grabowski et al., "Estimating the Effects of Regulation on Innovation: An International Comparative Analysis of the Pharmaceutical Industry", J. Law Econ. 21(1), 133–163 (1978).*
9. *AstraZeneca Press Release, "Alzheimer's, Cancer and Rare Disease Research to Benefit from Landmark MRC-Astrazeneca Compound Collaboration", www.astrazeneca.com (October 2012).*
10. *Pfizer Press Release, "Humana and Pfizer Form Research Partnership to Improve Health Care Delivery for Seniors", http://press.pfizer.com (October 2011).*
11. *TB Alliance Press Release, "Novartis Provides Drug Candidate Compounds to TB Alliance", www.thalliance.org (August 2014).*
12. *M. Langley and J. D. Rockoff, "Drug Companies Join NIH in Study of Alzheimer's, Diabetes, Rheumatoid Arthritis, Lupus", Wall Street Journal, http://online.wsj.com (3 February 2014).*
13. *B. Munos, "Lessons From 60 Years of Pharmaceutical Innovation", Nat. Rev. Drug Disc. 8, 959–968 (2009).*
14. *C. Ornagh, "Mergers and Innovation in Big Pharma", Int. J. Ind. Organ. 27(1), 70–79 (2009).*

Duncan Emerton is Senior Director, Syndicated Insights & Analysis at FirstWord. London, UK.

Making Pharmaceuticals

Research to Finished Product

Source
Manufacture
Outsource

- Pharmaceutical Ingredients
- Good Automated Manufacturing Practice (GAMP®)
- Scale-up: Qualification & Validation
- Supply Chain Risk Management
- The Future of Pharma in the UK

Register Online Today

Exhibition & Conference

NMM Exhibition Centre, Birmingham

28-29 April 2015

Supported by:

BCMPA · CQI · IPEC · Institution of Mechanical Engineers · pharmig · University of Leeds

Media Partners:

epm · manufacturing CHEMIST PHARMA · PHARMA · Pharmaceutical-Tech.com · the Medicine Maker

Making Pharmaceuticals

www.makingpharma.com

FREE to Attend

Engineering Success

Sitting Down With…
Andy Skibo, Executive Vice President, Operations at MedImmune, and Chairman of the International Society for Pharmaceutical Engineering (ISPE).

How did you get into your field?

I got my start in R&D at Monsanto in the 1960s. I put my chemical engineering degree from MIT to use developing car windshields and bulletproof glass for helicopters and planes being used in the Vietnam War. I first got involved in the pharma industry in the late 1970s, when I took at a job at Daniel Construction and Engineering to head up the new process engineering department of this new engineering division. My first assignment was to build a new pharmaceutical plant for Eli Lilly in Ireland. Next, I worked on a Roche project in Puerto Rico. I was hooked, and the majority of my projects since then have been in pharma.

What's kept you working in the pharmaceutical industry?

What I've always enjoyed about the pharmaceutical industry – particularly biologics – is that whatever your role, you're never far from the technology. It's a business where a complex technical issue will be solved by a group that includes our youngest, brightest technical people from the lab all the way up to the grey hairs like me who will be sitting around the boardroom table, delving back into 40 years of experience. You are totally integrated as a team from top to bottom and I find that very energizing.

How have the challenges changed over the years?

Back in the early 1980s, I was with Genentech when we built the first large-scale mammalian cell culture plant. It was so new that we put up canvas around the half-completed building to hide the size of the holes for the bioreactors; no one would have believed that we could operate at that scale. Now, the core challenge is planning for capacity – what I call nine dimensional chess. The range in demand for oncology immunotherapy can differ by as much as 17 times. Now take a dozen products like this: do you need four plants or do you need a quarter of a plant? At $800 million a throw, that's an investment decision you don't want to get wrong. But there are no textbooks to give you the answers. We have built very sophisticated planning models, but we had to invent those models. I love that complexity – it's what wakes me up in the morning.

How did you get involved with ISPE?

This is my first stint as Chairman but I have been on the board for 20 years and been involved with ISPE since before it was ISPE. To me the value of the Society is the network. It really plugs you into the industry. Before I start any major new project or make a difficult decision, the first thing I do is pick up the phone and call my peers – ISPE is one of the best platforms to get immediate exposure to valuable contacts. The ability to meet at the conference, or look at our online directory, and speak to people who have faced a similar problem to yours is worth its weight in platinum.

What are the key goals for ISPE in 2015 and beyond?

The last few years have been challenging for ISPE. ISPE's original founding and heavy growth period in the 1980s and 90s was based on large investment in pharmaceutical capital facilities, mostly in small molecules. There was a heavy demand for engineering and manufacturing talent to get these facilities licensed and running. When that capital investment curve went flat, we needed to find a new business model.

First, we will be heavily shifting our focus to include more biomanufacturing. Right now, half of the industry pipeline is made up of biologics and I have seen projections suggesting that this could rise to 75 percent by 2020. But currently over 80 percent of our members work in small molecule manufacturing. They have strong skills in the industry, just not in biologics, so why not help those members transition into a career in biomanufacturing?

"What I've always enjoyed about the pharmaceutical industry – particularly biologics – is that whatever your role, you're never far from the technology."

Second, for the industry as a whole, emerging markets are one of the main pillars of growth, so we want to help our members move from building a plant in the UK or US, to building one in China or Russia or the Middle East. Some emerging markets have real quality or regulatory issues and we also want to work closely with the regulatory agencies in those countries to help them understand what is involved in making a high-quality pharmaceutical plant.

How can we improve quality standards in emerging markets in the long run?

I believe we need a global quality network, with all countries adhering to the standards of highest quality that we take for granted in the US and Europe. At the moment, the problem is not just that products do not meet quality standards, it's a lack of acceptance in some emerging markets that these standards are necessary.

What's been your proudest achievement?

I have helped launch at least four new medicines and nothing gives you a greater sense of why we're in this industry. At Genentech, they used to hand out flags on launch day and I still have every single one.

Catalent®
MICRON TECHNOLOGIES

best technologies.
broadest expertise.
faster development.

NEW
Catalent Acquires Micron Technologies
LEADER IN PARTICLE SIZE ENGINEERING

OSDrC® OPTIDOSE™ TECHNOLOGY
RP SCHERER SOFTGEL TECHNOLOGIES
ZYDIS® FAST-DISSOLVE TECHNOLOGIES
CONTROLLED RELEASE TECHNOLOGIES
OPTIMELT™ HME TECHNOLOGY

Our 18 R&D teams in 10 countries are now working on 500+ projects, applying multiple proven and innovative drug delivery technologies to help you deliver optimal release profiles, enhanced bioavailability and better dose forms—preferred by patients and payers.

TECHNOLOGY SPOTLIGHT

MICRON PARTICLE SIZE ENGINEERING TECHNOLOGIES

Optimized particle distribution, shape and size, for enhanced bioavailability, stability and manufacturability. Proven particle size engineering technologies and integrated analytical services.

DEVELOPMENT DELIVERY SUPPLY

Catalent. More products. Better treatments. Reliably supplied.™

us + 1 888 SOLUTION (765 8846) **eu** 00800 8855 6178 catalent.com

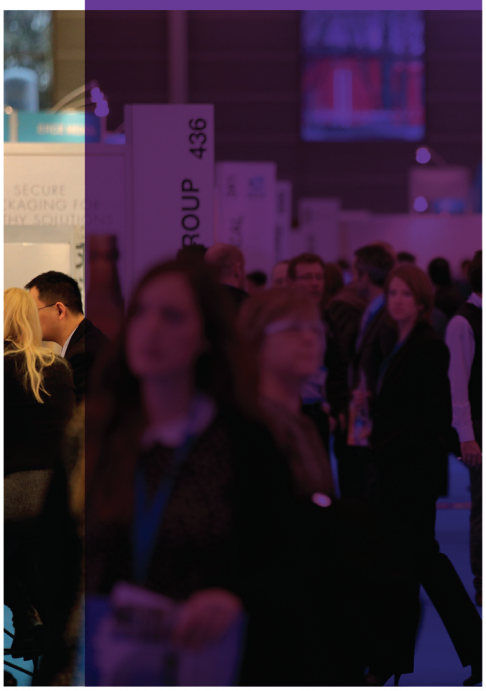
CTLT LISTED NYSE

TECHNOLOGY SELECTION & APPLICATION ▸ FORMULATION & ANALYTICAL SERVICES ▸ CLINICAL & COMMERCIAL SUPPLY ▸ TAILORED OR END-TO-END SOLUTIONS

Drug Delivery & Packaging
Pharmapack EUROPE

EXHIBITION & CONFERENCE **11&12 FEBRUARY 2015 PARIS EXPO, PORTE DE VERSAILLES, HALL 5**

Innovation, Networking & Education in Pharmaceutical Packaging and Drug Delivery Technologies



14th EDITION FEATURING:

- **370 international suppliers** in packaging and advanced drug delivery technologies
- **3,300 senior level managers** from pharma companies expected
- **2 day conference** to hear about the latest market trends for packaging developments and new drug delivery systems
- **1 day Technical Symposium** dedicated to Serialisation, Track & Trace
- **Workshops** allowing an in-depth discussion in 360° on specific technical issues
- **NEW!** **A learning lab** to enable visitors to learn how to apply new concepts or tools to their projects
- **NEW!** **2 networking breakfasts** on the North American and Chinese markets
- **Innovation Gallery** showcasing recently launched products, organised by product category
- **The Pharmapack Awards ceremony** rewarding the most innovative solutions

#pharmapackeu

INDUSTRY ARTICLES, NEWS, WHITEPAPERS & EVENT PROGRAMME ON
WWW.PHARMAPACKEUROPE.COM

UBM

the Medicine Maker

SIGN UP NOW FOR FREE

Multiplatform Reach

App
iPad edition offers an engaging multimedia experience.
Available for free on the Apple Newsstand.

Website
Acts as a hub for both our content and our community.
Access to articles and multimedia elements, interact through comments.

Digital Magazine
The PDF version of the magazine replicates the print issue.
Accessible to a truly global audience.

Optimization for Mobile
Content is optimized for handheld devices.
Instant and easily accessible at any time.

Social Media
A strong presence on social media channels.
Provides valuable feedback for reader engagement and trend awareness.

Print
This version will ensure your marketing message has a true professional look and feel.
The printed version is free of charge in both Europe and the USA.

To subscribe go to
www.themedicinemaker.com/subscribe

Or email tracey.nicholls@texerepublishing.com