SEPTEMBER 2017 # 33

# the Medicine Maker™



## What's on the Box?

Serialization: Coming soon to a pharma package near you



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# Online this Month


*Calling all Equipment and Technology Innovators!*

Nominations for The Medicine Maker 2017 Innovation Awards will close on November 6, 2017.

What are the Innovation Awards? The Awards celebrate the groundbreaking new systems and technologies released onto the market during 2017, which are expected to enhance pharmaceutical development and manufacture. The winners will be showcased in the December 2017 issue of The Medicine Maker.

*To nominate an innovation, fill out the online form at: http://tmm.txp.to/2017/innovationawards. Or email the editor Stephanie Sutton, at Stephanie.sutton@texerepublishing.com.*

Criteria

- The innovation must have been released (or will be released) in 2017.
- The innovation must be expected to have a significant impact on bio/pharmaceutical development and manufacture.
- Any type of product or technology offering related to bio/pharmaceutical manufacturing is eligible, including but not limited to: equipment, instruments, software, innovative services, excipients and drug delivery technologies.
- Nominations are welcome from individuals, groups, organizations or vendors.

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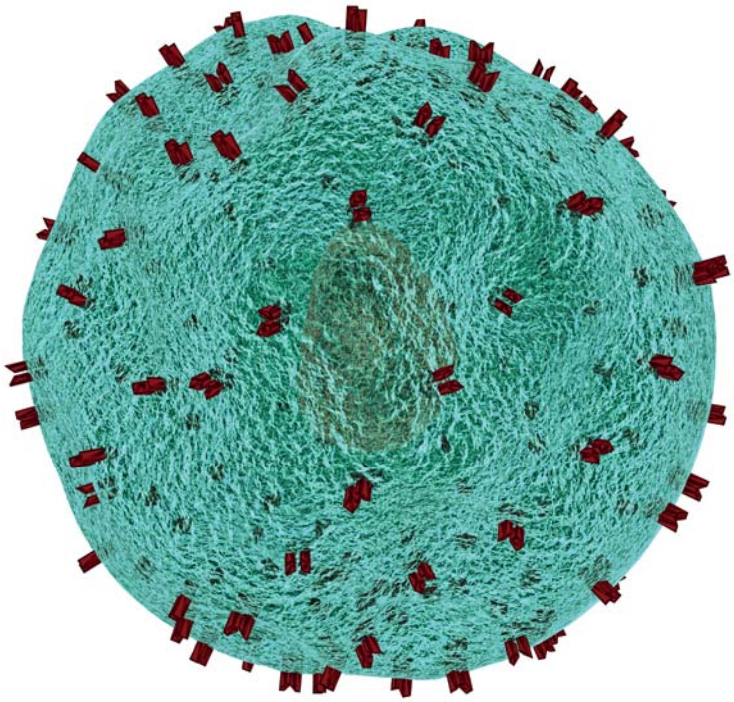

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## On The Cover

*Will pharma get its boxes in order in time for US and EU serialization deadlines?*

## Upfront




the Medicine Maker

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

*Associate Editor* - James Strachan
james.strachan@texerepublishing.com

*Associate Editor* - William Aryitey
william.aryitey@texerepublishing.com

*Content Director* - Rich Whitworth
rich.whitworth@texerepublishing.com

*Editorial Director* - Fedra Pavlou
fedra.pavlou@texerepublishing.com

*Publisher* - Richard Hodson
richard.hodson@texerepublishing.com

*Sales Manager* - Helen Conyngham
helen.conyngham@texerepublishing.com

*Head of Design* - Marc Bird
marc.bird@texerepublishing.com

*Junior Designer* - Hannah Ennis
hannah.ennis@texerepublishing.com

*Digital Team Lead* - David Roberts
david.roberts@texerepublishing.com

*Digital Producer Web/Email* - Peter Bartley
peter.bartley@texerepublishing.com

*Digital Producer Web/App* - Abygail Bradley
abygail.bradley@texerepublishing.com

*Audience Insight Manager* - Tracey Nicholls
tracey.nicholls@texerepublishing.com

*Audience Project Associate* - Nina Duffissey
nina.duffissey@texerepublishing.com

*Traffic and Audience Associate* - Lindsey Vickers
lindsey.vickers@texerepublishing.com

*Traffic and Audience Manager* - Jody Fryett
jody.fryett@texerepublishing.com

*Social Media / Analytics Associate* - Ben Holah
ben.holah@texerepublishing.com

*Events Manager* - Alice Daniels-Wright
alice.danielswright@texerepublishing.com

*Marketing Manager* - Katy Pearson
katy.pearson@texerepublishing.com

*Financial Controller* - Phil Dale
phil.dale@texerepublishing.com

*Accounts Assistant* - Kerri Benson
kerri.benson@texerepublishing.com

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

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

Change of address:
nina.duffissey@texerepublishing.com
Nina Duffissey, The Medicine Maker,
Texere Publishing Ltd, Haig House, Haig
Road, Knutsford, Cheshire, WA16 8DX, UK

General enquiries:
www.texerepublishing.com
info@texerepublishing.com
+44 (0) 1565 745200
sales@texerepublishing.com



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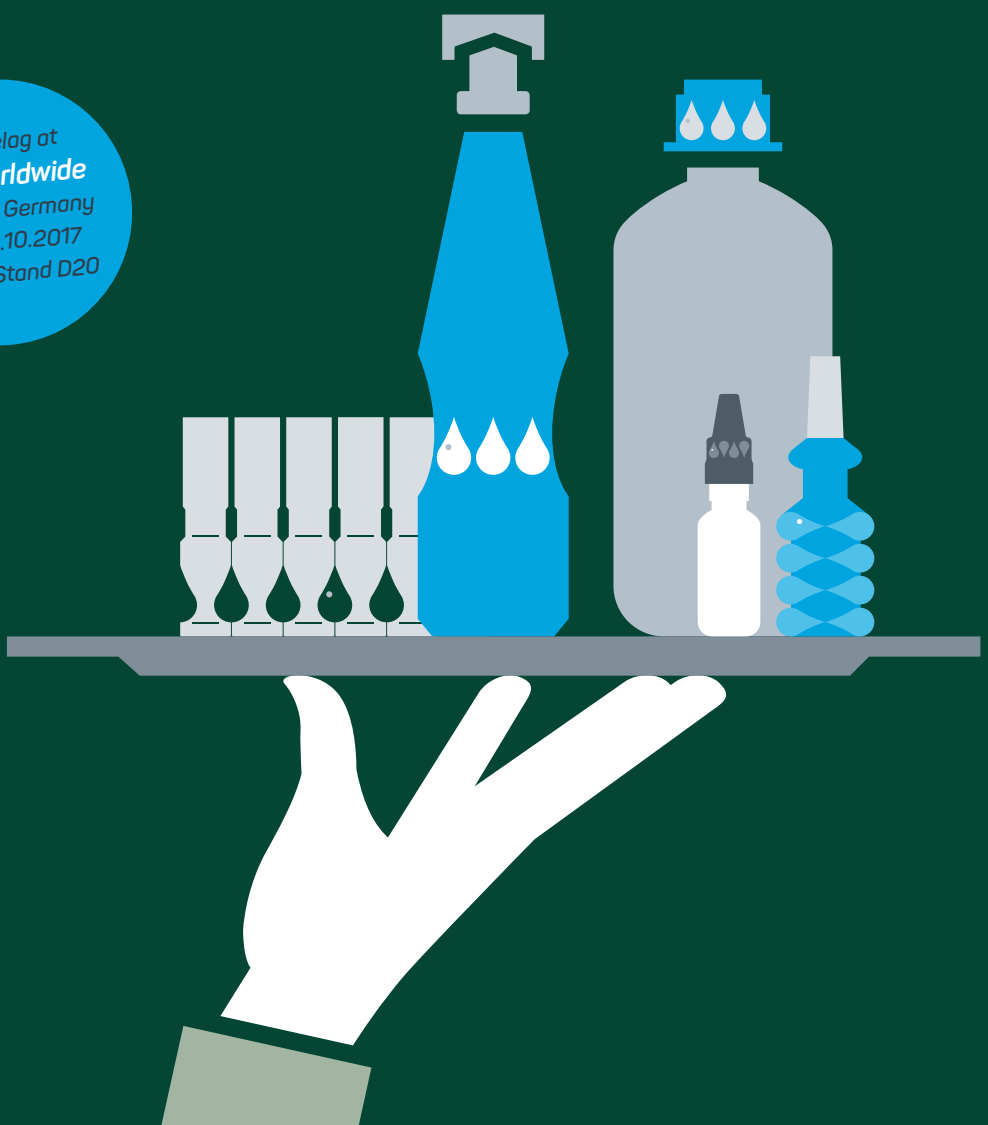


## In My View



## Feature



## Reports

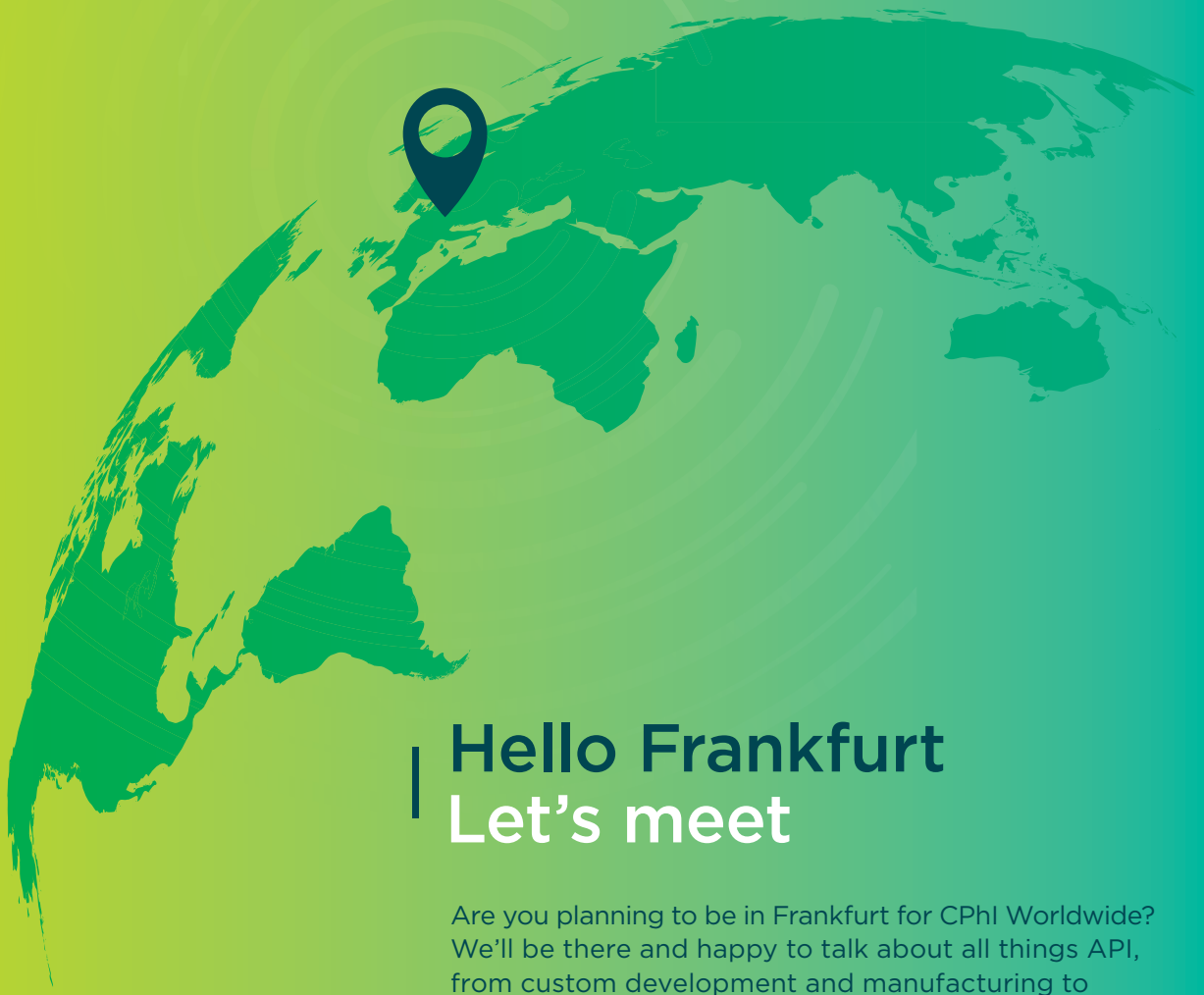


## NextGen



## Sitting Down With

**CPhI Worldwide**
**Frankfurt**
24–26 October 2017



# Hello Frankfurt
# Let's meet

Are you planning to be in Frankfurt for CPhI Worldwide? We'll be there and happy to talk about all things API, from custom development and manufacturing to generics and controlled substances.

It's a great opportunity to connect in person and meet the **experts you'll enjoy working with** at Hall 8, Stand 80G40.

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# Here's to Shared Successes!

*The Medicine Maker celebrates its third birthday – and the exciting changes shaping drug development*



The first issue of The Medicine Maker went to print in September 2014. Back then, we were passionate about reporting on the personalities shaping drug development and manufacture (and we still are!) – but there was some apprehension. Was there any space for a new voice? Would the industry enjoy reading the stories we wanted to tell? Three years and 33 issues later, we are still very much here, so the answer was evidently "Yes!" to both questions. Over that time, I have felt honored to share the stories of industry experts and scientists – from Nobel Prize winning scientist David Baltimore, to supply chain expert Martin Van Trieste, to a driving force behind the UK's cell therapy manufacturing activity (1–3) – the late Richard Archer, who sadly passed away in 2016.

As well as showcasing personalities and achievements, we have also reported on some of the biggest breakthroughs in drug development. Three years ago, there was no malaria vaccine, no cure for Hepatitis C, and no approved CAR-T therapy – in fact, there was still skepticism about whether CAR-T therapies would ever make it to market at all, and whether big pharma would embrace the development and manufacturing challenges of advanced medicines. It is still early days for CAR-T therapies, but there's plenty of optimism.

On the manufacturing side, equipment and technologies continue to advance, and we love showcasing the top technologies every year in The Medicine Maker Innovation Awards (4). Right now, there is much attention focusing on drug costs, and how more efficient manufacture and facility usage can make the most expensive medicines – biopharmaceuticals – more accessible. Some companies are considering the move to continuous bioprocesses in a bid to decrease manufacturing footprints, be more flexible, and improve product consistency. And though efforts and technologies are in the early stages right now, it will be interesting to see how they pan out – and how regulators react.

A big change on the near horizon is showcased in this month's cover feature on page 26. Serialization initiatives have been under discussion for years, but crunch time is close. The changes will likely bring some confusion, hopefully consolidation, but ultimately will lead to safer supply chains for all.

We will continue to track the pharma industry's evolution – and I am in no way concerned about a dearth of material. Of the many conversations I have had with industry stakeholders recently, there is a consensus that the industry is at tipping point for several important breakthroughs. Exciting times lie ahead, and The Medicine Maker is happy to join you on the journey.

**Stephanie Sutton**
*Editor*

*References*

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2. *M Van Trieste, "Global Vigilance", The Medicine Maker, 27, 20–27 (2017). Available at: http://bit.ly/2l8gbi2.*
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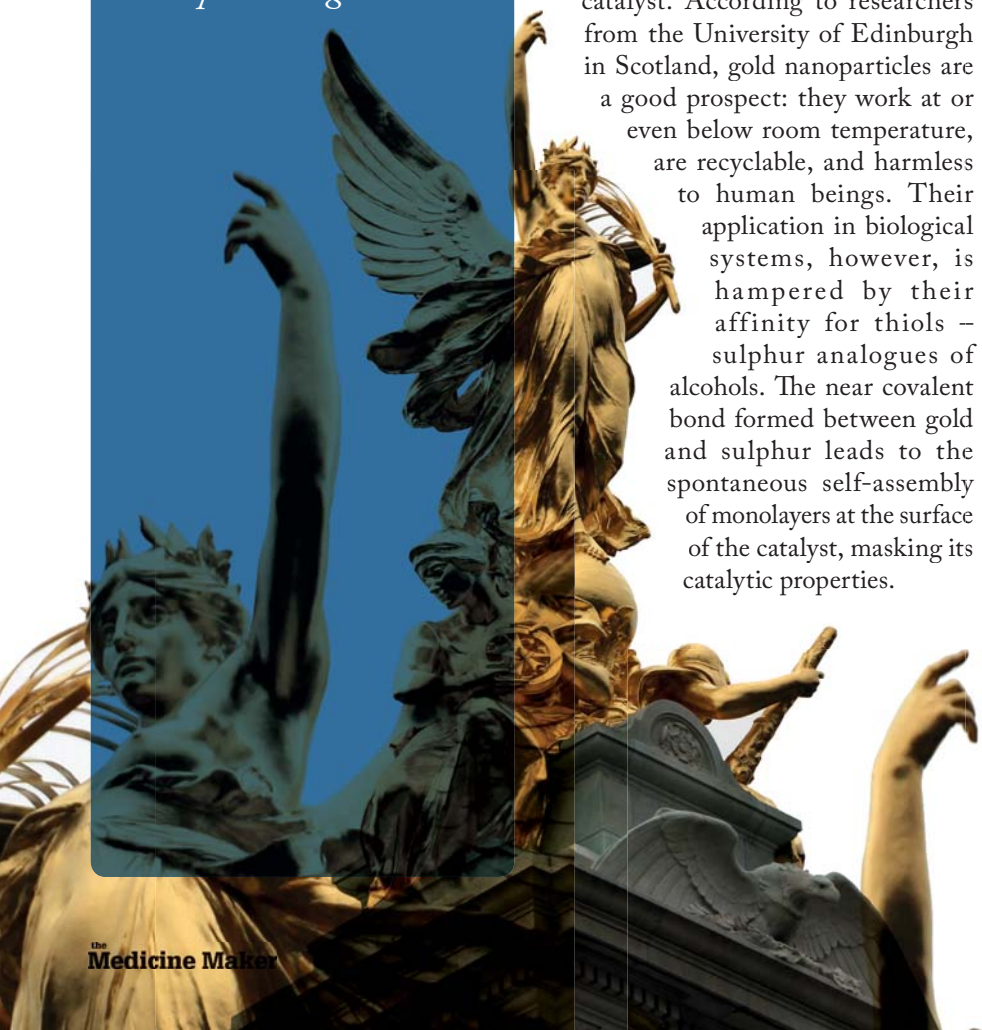
# Upfront

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

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



## The Golden Touch

**Researchers move a step closer to improving the effectiveness of cancer drugs by "manufacturing" therapeutic compounds in-vivo using gold nanoparticle catalysts**

For decades, scientists have been trying to figure out ways of reducing the toxic side effects of chemotherapy drugs. But what if patients could receive inactive chemical precursors along with a catalyst to produce therapeutic compounds at the site of the tumor?

The trouble is finding the right catalyst. According to researchers from the University of Edinburgh in Scotland, gold nanoparticles are a good prospect: they work at or even below room temperature, are recyclable, and harmless to human beings. Their application in biological systems, however, is hampered by their affinity for thiols – sulphur analogues of alcohols. The near covalent bond formed between gold and sulphur leads to the spontaneous self-assembly of monolayers at the surface of the catalyst, masking its catalytic properties.

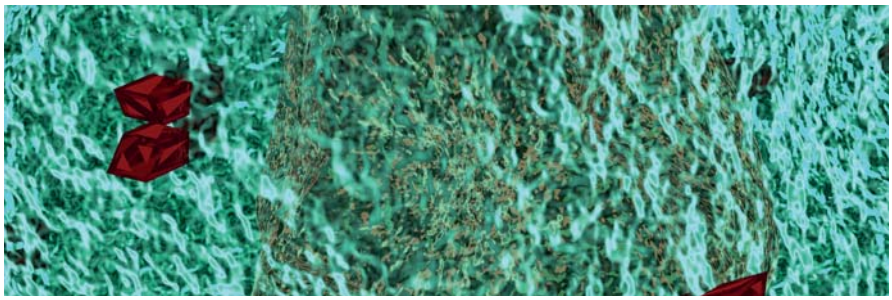
Asier Unciti-Broceta, Reader in Innovative Therapeutics at Edinburgh, and co-author of a recent study (1), has been able to protect gold nanoparticles from thiols within a polymeric device – a PEG-grafted low-crosslinked polystyrene matrix – allowing gold to work as a catalyst even in the presence of serum proteins (which are rich in thiol groups).

"We have demonstrated the potential of our therapeutic device by manufacturing chemotherapy drugs in the presence of cancer cells," says Unciti-Broceta. The nanoparticles have also been tested in a living system, with Unciti-Brocera and his co-authors demonstrating the locally-controlled release of a florescent dye in the brain of a zebrafish. "This opens up new avenues both in therapy and biomedicine, as we can now release drugs, probes or biomolecules in specific locations within the most complex and sensitive organ with spatiotemporal control," says Unciti-Broceta.

The researchers are now working with neurosurgeons and urological surgeons to use gold implants in cancer treatment. "We are currently investigating a two-component strategy consisting of surgical implantation of gold devices inside locally-advanced cancers; for example, brain tumours, and then giving inactive starting materials that will be converted into active anti-cancer drugs after reacting with the gold inside the tumor," he explains. "The chemotherapy drugs will be 'catalytically' generated just within the tumor, so the side effects of the chemotherapy in healthy organs will be minimal, and the treatment will last as long as the patient keeps taking the drug precursors." *JS*

*Reference*

1. *AM Perez-Lopez et al., "Gold-triggered uncaging chemistry in living systems", Angew Chem. Int. Ed. Engl., [Epub ahead of print] (2017). PMID: 28699691.*



# Making Therapeutic History

## The wait is over: the FDA gives a 'thumbs-up' to the first CAR-T therapy

"We're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer." So said FDA Commissioner Scott Gottlieb, commenting on the landmark FDA approval for a CAR-T cell-based gene therapy (1). Novartis' Kymriah (tisagenlecleucel) was approved at the end of August to treat pediatric acute lymphoblastic leukemia (ALL) – a cancer of the bone marrow and blood. Gottlieb added, "New technologies such as gene and cell therapies hold out the potential to transform medicine and create an inflection point in our ability to treat and even cure many intractable illnesses."

What does the Kymriah treatment involve?

i. The patient's own white blood cells are removed, cryogenically frozen, and shipped to a Novartis site.
ii. Monocytes and B-lineage lymphoblasts are separated (after thawing).
iii. T cells are activated with an anti-CD19 CAR transgene, which gives them the ability to seek out and destroy cancerous cells that express CD19.
iv. T cells are expanded, washed, cryogenically frozen, and sent back for reinjection into the patient.

The approval is considered an important regulatory milestone for the CAR-T field. Public Affairs Specialist for the FDA, Andrea Fischer, says, "The approval pathway for Kymriah was essentially the same as other biological products requiring licensure. However, the FDA did grant Kymriah Priority Review and Breakthrough Therapy designations – meeting with the sponsor throughout its development and clinical trials."

Eric Althoff, Head of Global Relations at Novartis, adds that Kymriah was approved more than a month ahead of the October 3 approval deadline – and the company isn't done yet. "Novartis plans additional filings for Kymriah in the US and EU later this year, including applications for the treatment of adult patients with r/r diffuse large B-cell lymphoma (DLBCL)," says Althoff. Novartis are also working on a number of other CAR-T therapies, in collaboration with the University of Pennsylvania, to treat multiple myeloma, glioblastoma, ovarian cancer, and more.

Though Kymriah is the first CAR-T approval, other companies, such as Kite Pharma, are hot on Novartis' heels, so it's unlikely to be the last. *WA*

*Reference*

1. *FDA, "FDA approval brings first gene therapy to the United States", (2017). Available at: http://bit.ly/2grlPdB. Accessed September 12, 2017.*

# Leaving on a Jet Plane

**At the end of October, thousands of industry experts will flock to Germany for one of Europe's largest pharma trade shows**

What?
CPhI Worldwide is an annual trade show. First held in Frankfurt in 1990, the event originally focused on ingredients and intermediates; since then, CPhI has expanded to cover outsourcing, machinery, and packaging, as well as the latest trends and regulations shaping the future of the pharma industry. Additional CPhI events are also held around the world throughout the year.

When?
The main trade show runs October 24-26, 2017, with a Pre-Connect Congress, focusing on exploring the future of pharma, being held on Monday, October 23.

Where?
Congress Center Messe Frankfurt, Germany.

What's On?
- Four other events are co-located with CPhI: ICSE (outsourcing), InnoPack (packaging), P-MEC Europe (capital equipment and

instrumental analysis), and Finished Dosage Formulation.

- October 23 – Pre-Connect Congress, featuring keynotes from Samsung Biologics President and CEO, Tae Han Kim, and Ajaz Hussain, President, National Institute for Pharmaceutical Technology & Education, and the former Deputy Director of the FDA Office for Pharmaceuticals.
- October 24 – Women in Leadership Forum, where women can meet and discuss the promotion of diversity in the workplace, while sharing their experiences.
- October 24 – The release of the 5th CPhI Annual Industry Report. This eagerly anticipated collection of essays will provide thought leadership on the industry's hottest topics and issues.
- October 24 – Announcement of the winners of the 2017 CPhI Pharma Awards. The awards honor companies and individuals driving the pharma industry forward through innovations, technologies and strategies.
- October 24-26 – The Pharma Insight Briefings are a series of seminars on specialist topics and regional updates from big pharma, industry associations, market intelligence agencies, and more.
- October 24-26 – An Innovation Gallery will showcase some of the most exciting products on display at the show, and Innovation Tours will run across each of the three days (registration is free, and is first come, first served basis).

## CPhI 2016 in Barcelona

Had a record attendance of over

**42,000**

An **18%** increase compared with the 2015 event

More than **2,550** exhibitors from 156 countries

The top visitor job title was CEO/Vice President/Director/General Manager **47%**

Top 3 objectives for visiting:

- Meet existing suppliers/partners **88%**
- Find new partners **73%**
- Find/source new suppliers **51%**

# Bright Spark

## Using electrochemistry to boost manufacturing and drug discovery

Vicinal diamines are structural motifs frequently found in pharmaceuticals – with penicillin, Tamiflu and many anti-cancer agents being prominent examples. Their wide use has motivated researchers to develop an efficient way to prepare the motifs, but so far this has proved tricky.

"Elegant methods have been developed for making vicinal diamines of specific structures, but a unified approach to their synthesis remains elusive," says Song Lin, researcher at the Department of Chemistry and Chemical Biology at Cornell University. "This is challenging because a general and efficient way for making vicinal diamines is to directly install two carbon-nitrogen bonds onto an olefin; however, this process usually requires esoteric reagents or heavy metal catalysts, which are not sustainable and difficult to use on practical scales."

To that end, Lin and his team set out to develop a practical and more environmentally friendly approach to manufacturing vicinal diamines, using a combination of electricity and a manganese catalyst to convert alkenes and sodium azide – both readily available feedstocks – into 1,2-diazides. The resultant 1,2-diazides were then smoothly reduced to vicinal diamines in a single step using standard protocols with high chemoselectivity (1).

Electrochemistry has yet to be broadly applied in organic synthesis, according to Lin; one reason being it can be challenging to work out which reaction conditions will allow electrochemistry and the molecular catalysis to act together in the correct manner. But the technique does offer the advantage of allowing researchers to fine-tune their reactions by altering the voltage, and thereby the electrical oxidation potential of a given reaction component. Such control allows researchers to target specific components, without disturbing other functional groups.

"We hope people will start to use this potentially enabling technology in both the large-scale manufacturing of drugs and also in the laboratory discovery of new medicines," says Lin. *JS*

*Reference*

1. *N Fu et al., "Metal-catalyzed electrochemical diazidation of alkenes", Science, 357 (6351), 575-579 (2017). PMID: 28798126.*

# Business-in-Brief

**Keeping close ties, locking-up loopholes, and calculating costs… What's new for pharma in business?**

## Regulation

- FDA Commissioner Scott Gottlieb has announced FDA plans to close a legal loophole that allows companies to avoid pediatric study requirements. The loophole is an unintended consequence of two US bills: the Pediatric Research Equity Act (PREA) and the Orphan Drug Act (ODA). PREA requires companies to study pediatric populations after approval, but if an approved drug for an adult population receives designation under the Orphan Drug Act to treat a subset of children, then it becomes statutorily exempt from PREA requirements. "It's a loophole that is in direct opposition to what Congress intended," says Gottlieb.
- The UK life sciences industry hopes to see the UK prioritize close ties to the EMA post-Brexit. The report, published by the UK Life Sciences Industrial Strategy Board, argues, "the UK market is too small even with the fastest and most innovative regulatory system in the world, to stand alone from a larger decision-making bloc," despite the MHRA's record of driving innovation in the EMA. "Given the UK market size at around three percent of global pharmaceutical sales, a wholly free-standing system would likely be high cost – both in terms of efficiency and attractiveness to companies who typically apply to the largest markets first," wrote the authors.

## Manufacturing

- Eli Lilly is set to cut 3500 jobs – 8 percent of its global staff – and close several facilities in an attempt to save $500 million. The company expects the majority of the job loses to come from their voluntary early retirement program in the US. A research and development office in New Jersey, US, and the Lilly China Research and Development Center in Shanghai are also set to close. Lilly expects the closures, severance expenses, and the retirement program to cost $1.2 billion pre-tax.

## Controversies

- Allergan has transferred all patents for its billion dollar dry eye drug, Restasis, to the Saint Regis Mohawk Tribe. The New York based Native American Tribe agreed to grant exclusive licenses to Allergan in return for a $13.75 million payment, plus $15 million annual royalties. The controversial arrangement, if successful, would allow Allergan to avoid an ongoing challenge against the validity of its Restasis patents, because the tribe is recognized as a sovereign tribal government under US law and is immune from IPR challenges.
- Pharmaceutical companies in Australia gave AU$12 million to doctors, nurses and pharmacists between November 2016 and April 2017, according to a report. Health economists Philip Clarke and Barbara de Graff conducted an analysis for a newspaper and found, "the payments comprised more than $6.5m for travel expenses and accommodation; more than $4.2m in speaking and consultancy fees; and more than $700,000 to cover registration at medical conferences and events."

*For links to original press releases, visit the online version of the article at: www.themedicinemaker.com/0817/business*

# Cater to the Customer

**Efficacious and safe drugs often don't make it to market. But why? And what can you do about it?**

Why do drugs fail? Research shows that efficacy and safety are significant reasons – as you might expect. But one surprising statistic is that one quarter of failures at phase II and III are because of commercial or strategic reasons (1). In addition, a number of drugs, although meeting safety and efficacy endpoints, struggled post-approval for other reasons. Will Dunlop, Head of Market Access at Mundipharma International, set out to find an explanation and embarked on a recent study with Nektarios Oraiopoulos, Judge Business School, to identify the key barriers to a customer-focused drug development process, and then set out a comprehensive framework to overcome them (2). Here, Dunlop tells us more.

What are the most important factors in preventing commercial or strategic drug failures?

Collaboration between R&D, commercial and market access teams is crucial to the success of a drug. It's well reported that payers are playing an increasingly important role in the success of a medicine – and regulatory approval can no longer be considered a guarantee for market success and profitability. Given the increasing budgetary pressures payers are under, pharma companies quite rightly have to demonstrate the benefit of new medicines when compared with existing standards of care. Global healthcare systems cannot afford innovation for

innovation's sake anymore. Companies must have a vision in mind of the difference their therapies will make, and only look for innovations that address both payer and patient needs.

Do you have any specific examples of strategic failures?

Exubera is an example of a good drug that met regulatory requirements, but was widely reported as being taken off the market due to low sales. The inhalable insulin product cost $5 compared to $2-3 for injectable insulin. In the US, many insurance companies refused to cover the cost of the more expensive treatment; and in the UK, NICE argued that Exubera should only be approved for diabetics with a proven fear of needles.

Can you sum up the main barriers to successful internal collaboration, and your proposed solutions?

The report that we developed in partnership with Cambridge Judge Business School revealed that good science is simply not always enough to get a product to the patient who needs it. We concluded that the main barriers to collaboration can be divided into economic, organizational and behavioral ones – each bringing unique challenges.

Economic barriers to collaboration are linked to the substantial timeline required to develop a new therapy. R&D teams are often, understandably, focused on driving their product to the next stage without ensuring it's the right decision overall. Too many times, we've seen these drugs go on to fail at a later stage, when hundreds of millions have been invested.

There are also behavioral barriers to collaboration where scientists have invested a lot of time into a compound and become such strong believers in it that they fail to acknowledge the evidence against it. Understanding that this behavioral bias exists and seeking advice from experts is key to overcoming it.

Organizationally, there is often an insular culture in which people work closely with and learn only from their own group. Having goals that require a collective effort from all departments forces teams to work together more effectively.

What is the most important thing to consider when developing a commercial strategy?

The most important thing is that you really understand the market in-depth at a local level; you need to look through the lens of each of your stakeholders – what does the payer need to see? What will the patient want? What does the health system require? Shaping your strategy around these insights and improving the communication flow between R&D, commercial and market access teams, coupled with strong science, is a good recipe for success.


*References*

1. *RK Harrison, "Phase II and phase III failures: 2013–2015", Nat Rev Drug Discov, 15 (12), 817–8 (2016). PMID: 27811931.*
2. *N Oraiopoulos and WCN Dunlop, "When science is not enough: a framework towards more customer-focused drug development", Adv. Ther., 34 (7), 1572–1583 (2017). PMID: 28625003.*

# In My View

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

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

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

## Don't Touch That Data

**Not everyone in your organization understands or cares about data integrity – but they should.**

*By Mark Stevens, Managing Director, Formpipe Life Science (UK).*

Data is omnipresent in the pharma industry. From creation, to deletion, to preservation – and everything in between – data integrity is the bedrock of GLP, GCP and GMP. But what exactly do we mean by safeguarding data integrity? Essentially, there are two core elements: physical and logical. Physical refers to aspects such as (physical) location, personnel access controls, and processes for retrieving or moving the data sources. Logical refers to the controls and records relating to any access and use of the electronic data after it has been created, as well as being able to demonstrate the accuracy and completeness of the data.

In recent years, there have been several high-profile cases in the US where quality control analytical testing results and data have been deliberately manipulated to falsify test results associated with the release of medicinal products (1, 2) . In turn, regulators, as well as the wider quality community, have been forced to prioritize the restriction of quality-related processes and systems that give users the opportunity to manually modify data, whether deliberately or inadvertently. To be very clear, most instances of poor data integrity result from human error or negligence, rather than malice. Nevertheless, the consequences of the action remain the same. Corrupting the continuity and completeness of an audit trail – whether by altering or removing pages of a physical record and/or replacing them with alternatives, or by altering or deleting electronic records and not being able to reconcile this with who, why, when, or under what authority, for example – irreparably compromises integrity; confidence in the quality of the record is subsequently lost, and demonstrating compliance to inspectors suddenly becomes extremely difficult. Not to mention the reputational damage once the media find out…

With a continuing move towards more distributed workforces, there has been an increase in the use of technology (particularly mobile devices) to capture data and, in the pharma industry, interact with the electronic quality management systems (EQMS) that handle the data. During the past 24 months, the industry has seen an increased number of published guidance papers and regulations regarding data integrity, such as The WHO's Guidance on Good Data and Record Keeping Management Practices, published in September 2015, and the FDA's Data Integrity and Compliance with GMP Guidance for Industry, published in April 2016. Regulated organizations need to demonstrate how they are maintaining data integrity with the increased use of mobile devices, hosted applications and

*"Most instances of poor data integrity result from human error or negligence, rather than malice."*

distributed workforces. The challenge the industry faces is how to embrace the advantages such technology provides, without compromising data integrity – and ultimately patient safety.

Any technology, however sophisticated, will never be a total solution in isolation. Organizations that fail to fully recognize the role that data integrity plays in promoting safe and profitable practices, regardless of the technology used, are leaving the door open to risk. A good data integrity strategy should incorporate three elements: people, processes, and technology.

Ownership should also rest with every individual who encounters the data. There is an onus on everyone involved in the preparation, recording, checking, transferring, storage and use of GxP data to understand and adhere to the internal processes and regulations associated with maintaining data integrity. Those people involved should also challenge anything that represents a potential risk to data integrity – and be aware of the consequences if integrity is compromised, as well as the benefits of effective data management, whether paper or electronic.

Most problems associated with data integrity occur at the interfaces between systems and at the points of manual data input. The best people to understand any weak points, manage the risks, and drive improvement are those that work with the processes every day. Championing data integrity or improving practice does not always require financial investment and/or increased auditing. Often, small, cultural changes, such as instigating reward and recognition programs, appointing data integrity champions, and holding regular refresher courses on best practice, can instill a sense of context and responsibility in all staff. Often, just communicating the importance and potential impact people have in the context of their specific roles and tasks can make a huge, positive impact. If people are not clear on why data is monitored and measured, or do not feel empowered to challenge processes, how can they be expected to care about it? Equally, if methods of managing quality assurance and safeguarding data integrity are outdated or ineffective, how can organizations expect to remain compliant?

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# Out with the Old, in with the New?

**Not quite. Tried and tested analytical approaches like ELISA aren't going away in the world of bioprocessing, but modern techniques allow for real-time analysis. Together, they present an orthogonal approach.**

*Alex Perieteanu is Director Biopharmaceutical Services - Life Sciences at SGS, Canada.*

There have been increasing calls from my company's global clients for bio-layer interferometry (BLI) – a real-time analytical technique for studying biomolecular interactions – to be incorporated as a routine quality control test in bioprocessing. At the moment, BLI is most commonly used in the research phase for high-throughput target screening, but I believe it is more than applicable for quality control and to ensure that products are consistent and stable from lot to lot. BLI can measure interactions between many different types of molecules, whether a pair of proteins (or multiple proteins), a protein and a small molecule or peptide, or even two different fragments of DNA. Light of a particular wavelength is emitted through a fibre optic probe or biosensor. The probes have a unique chemistry, and multiple different chemistries are available commercially. When a molecule of interest binds to the coated probe there is a measurable change in the wavelength of the light, giving the ability to monitor on and off binding kinetics in real-time.

BLI's flexibility in experimental design and industrial applicability parallels that of the classical enzyme-linked immunosorbent assays (ELISA). Conceptually, BLI differs from ELISA only in the mode of detection, so ELISA methods can usually be easily transferred to BLI. In practice, the major difference is that the ELISA coating and binding steps are blind, making it difficult to gauge exactly how effective they are; optimization is really only possible based on the end results. BLI, on the other hand, enables a real-time understanding of binding, whether it be during coating or molecular interaction, and is generally more sensitive with a larger dynamic range. The advantage of seeing the binding in real time is that it gives greater insight into the binding kinetics and specificity. With ELISA, you obtain the binding affinity (the dissociation constant), but with BLI you don't just get the binding affinity, you generate it through its association and dissociation kinetics, so you not only see what is binding, but how fast.

ELISA's advantage lies in that it doesn't require significant capital expenditure and is a familiar technology. The pharma industry tends to favor tried and tested approaches, and ELISA certainly falls into that category, but BLI really does offer something more and is worth seriously considering. Clearly, ELISA, BLI and other analytical techniques, such as surface plasmin resonance (SPR), have their own particular strengths and weaknesses – and certain applications are simply better suited for different instruments. Speaking from my own experience, I see a slight trend towards the implementation of BLI over SPR, which could be because of perceived barriers to entry with SPR. However, I feel that BLI is highly complementary to SPR. From a business perspective, one might argue that they are competitive in nature but, scientifically speaking, the generation of complementary data sets using orthogonal techniques is always preferred. As such, a strong case can be made for the implementation of both techniques. I would also suggest that it is unlikely that any technique will ever completely take over from ELISA – just as there will always be an important place for a $1 pin prick diagnostic test in addition to an MRI scan.

*"I would also suggest that it is unlikely that any technique will ever completely take over from ELISA."*

Analytical technologies have advanced significantly over the last decade, becoming more sensitive and user friendly. It is to the benefit of all of us – since we are all patients – to have a range of orthogonal techniques in the analytical toolbox because the more we can understand products from a functional perspective, the better positioned we are to generate efficacious medicines.

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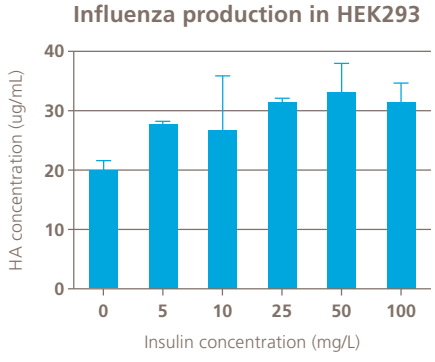


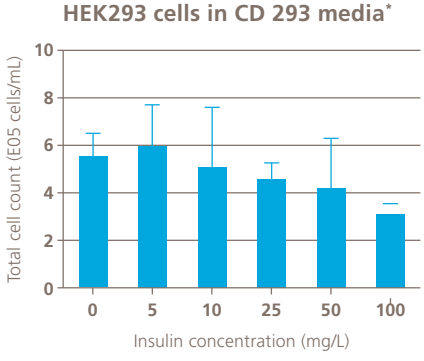


*Data kindly supplied by Aziza Manceur, National Research Council Canada. Hemagglutinin (HA) assay is used for quantification of Influenza (H1N1). Insulin Human AF used in the experiments is supplied by Novo Nordisk Pharmatech. CD 293 media is trademark of Thermo Fisher Scientific.

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# Collaborating to Get Biopharma in the Fast Lane

**Scaling up a bioprocess doesn't need to be a headache – especially when there are firms out there that can lend a helping hand.**


Patrick Guertin


Alex Tracy

Having been in the industry for more than 25 years, Patrick Guertin knows that cells can be temperamental and don't like to be rushed, but in today's biopharma industry speed to market is key. Guertin is a Global Technical Manager for GE Healthcare Life Sciences, where he focuses on upstream development and supporting the company's Fast Trak services for process development and manufacturing.

GE Healthcare is working with a number of biopharma companies to help them advance their bioprocesses, including Roivant Sciences. Roivant specializes in picking up abandoned drugs from other companies that still have great potential, and has recently collaborated with GE on an investigational orphan drug product – RVT-801. We speak with Guertin and Alex Tracy, Vice President of Pharmaceutical Development at Roivant, to learn more about the challenges of speed to market and the details of their collaboration.

What are the biggest challenges facing biopharma manufacturers today?

*Patrick Guertin:* Many companies are looking to optimize their bioprocesses and to move quickly from the development stage to clinic and, ultimately, to market – after all, time is money. The biopharma industry has matured a great deal over the past two decades and a plethora of new tools and technologies to aid the manufacturing process have been introduced, and yet scale-up can be a significant challenge. Cells can be unpredictable and can behave differently at large scale compared to lab scale.

Increasingly, biopharma companies are turning to service providers to help with the challenge. With GE's Fast Trak services, our job is to support the development of a robust process including upstream and downstream process development, analytical development, quality assurance, quality control, and cGMP manufacturing. My focus is primarily on upstream process development, which encompasses everything from clone identification, to media optimization, process design and scale-up. For clients, it often comes down to understanding what scale they need to be at for manufacturing. Often, we'll take a process that was developed in stainless steel and translate it into a single-use platform. I believe that flexibility is an advantage in biopharma production and that single-use systems can be a huge help in this regard since they facilitate scale-up, as well as help to reduce capital and operating expenditures. As an example, our bioreactors do not require steam-in-place (SIP) sterilization or clean-in-place (CIP). Also, they are scalable and can be used for a variety of process platforms, including mammalian, insect and microbial.

*"Increasingly, biopharma companies are turning to service providers to help with the challenge."*

*Alex Tracy:* The industry is seeing ever increasing titers coming out of cell cultures. On the one hand, it's great because it really reduces the overall manufacturing footprint, but it has clearly put some stresses on downstream unit operations. In time, the industry will have to learn to overcome this bottleneck, perhaps through better ligands and chromatography resins. Right now, it's perhaps a good problem to have as the shrinking of manufacturing processes has enabled greater uptake of single-use technologies. Single-use systems make it more economical to manufacture drugs that require smaller quantities, such as

drugs for orphan diseases. With RVT-801, for example, we are working at a relatively small volumetric scale.

How did Roivant and GE come to collaborate?

*PG:* Roivant's investigational enzyme therapy, RVT-801, is being developed for the treatment of acid ceramidase deficiency, an ultra-rare, lysosomal storage disease that manifests as Farber disease. Roivant had a pre-existing clone that was only running in hollow fiber bioreactors, which is challenging to scale up. Working with Roivant, we took a series of clones from them, selected the best producer and best grower, optimized the media/feeds, and then scaled the process up using our single-use bioreactor platforms. We manufactured the bulk drug substance in our cGMP manufacturing suite and now we are transferring to a third party for Phase III and commercial manufacturing. It has been a very efficient and rewarding collaboration – particularly since there is no treatment for Farber disease. The whole collaboration has been defined by mutual respect and appreciation, and we have had some very good discussions with Roivant about what they thought they were getting in terms of product per volume per time in their original manufacturing platform, versus what we thought we could achieve with our bioreactor technology, which offered more flexibility in terms of scale-up.

*AT:* We actually inherited the partnership with GE Healthcare. Roivant obtains its assets through partnerships or acquisitions. Often we acquire compounds from large pharma companies who have already conducted Phase II trials, but aren't planning to progress the molecule any further. We identify the promising molecules that we believe have a chance to make it to market and then we launch subsidiary companies to develop those molecules. RT-801 is being handled by our subsidiary, Enzyvant, for example.

When we acquired RVT-801, GE Healthcare had already been involved with the enzyme and its original developer, so it was perfectly natural to continue the work with them. For me, it's been really interesting to continue my relationship with GE because I've been working with their systems since I was in graduate school. They are well known for their quality products and stability of supply. Since they have been involved with RVT-801 for a long time, the team at GE is also really engaged in the work and what it could mean for patients. RVT-801 has been granted orphan drug designation by regulatory agencies in the United States and the European Union.

Working in the rare disease space is incredibly rewarding. With Farber disease, patients are deficient in the enzyme that breaks down ceramide – ceramides then accumulate at the cellular level leading to the formation of subcutaneous nodules, inflammation, and joint contractures that present similar to juvenile idiopathic arthritis. Acid ceramidase deficiency can also cause spinal muscular atrophy with progressive myolonic epilepsy. Most patients are children and those that are severely affected do not have a long lifespan. It's easy to become passionate about something when you see kids suffering. Enzyvant has been conducting a natural history study of patients with Farber disease to better define the natural course of disease and the relationship between specific symptoms, biomarkers, and prognosis. With respect to the product, we are focusing on a specific epitope – mannose 6 phosphate on the glycan structure that allows the protein to be internalized and correctly targeted. From our standpoint, having the protein with the correct glycosylation pattern is essential.

What are the main challenges associated with scaling up a bioprocess?

*PG:* I've seen a lot of companies with limited understanding of their process and insufficient relative data, which can lead to problems when moving from the lab to the commercial scale. You need to be asking, how are you controlling the critical process parameters? How does the process impact the molecule? And how can you align yourself with state-of-the-art technologies, and use them for the right processes?

*AT:* We were fortunate with RVT-801 in that we have a relatively well-behaved and stable enzyme – we haven't had too many bioprocessing challenges to overcome, although we do need to be careful with the feed strategy for

this particular cell line because of the high densities.

The amount of material required by the non-clinical group, however, has been another story. Farber disease is an ultra-rare disease that only impacts a handful of patients worldwide. Because the disease is so rare, we have a relatively small number of people recruited for clinical trials and we only need a very small amount for our first-in-human clinical studies. From a non-clinical perspective, the enzyme has been really well tolerated in toxicology studies and it has required a tremendous amount of material – which has been a surprise. I've had to dedicate a number of runs to produce the required amount of enzyme and I wasn't quite prepared for it! In the long run it will be a positive, since it should give us a good therapeutic window to work with – and hopefully greater chances of clinical success for the future.

And what about technology transfer?

*PG:* It is vital to get technology transfer right to ensure smooth, rapid development. To ease the process, it's worth normalizing the engineering metrics of the system in which you're producing, such as the power input or mass transfer. Perhaps the most important element is communication and transparency. Working with a service provider is all about the relationship and you need a single point of contact. One of the benefits with our Fast Trak team is that we have a global footprint. For example, a client may come to us with a fragile process, which we transfer to our site in the US. The client may then wish to transfer the process to China. Because we have a team in China too, the two teams can collaborate and coordinate in terms of documentation and procedures.

*AT:* Technology transfer is usually pretty challenging, but it's been pretty smooth so far. We've made three batches at GE at scale, put together a good initial package, and we think the product is suitable to take forward. There has been excellent dialogue between the two organizations and if there's another opportunity to work with GE then we will. Since GE is known to have a huge breadth of experience in both upstream and downstream processing, you know you are going to get something that is ready for commercialization. The last thing you want is to invest in a partnership that still leaves you with substantial additional development is, at the end. Speed during development is, of course, important, but it's useless to develop something with a burst of speed and then find you have to redo everything. In any kind of outsourcing, the hardest part is finding the right partner – as Patrick said, the relationship is critical. When you have a good partner and both of you are pulling together to get the product on the market it's incredibly valuable – and difficult to assign a monetary value to.

## The Biosimilars Viewpoint

*By Patrick Guertin*

In recent years, we've seen an increase in the number of biosimilar customers – indeed, biosimilars are a key trend in the industry overall thanks to pushes from patients, regulators and manufacturers. The opening of the US market also has provided a much needed boost for the biosimilars field. A lot of new players are entering the field, but not all of them have the right skills to cope with complex bioprocesses, fuelling a need for external services and advice.

One of the big debates around biosimilars is how close the molecule has to be to the original (innovator) drug. You are never going to produce an exact copy of a biopharma molecule (and even the original biopharma drug will experience some batch to batch variability due to the nature of cells), but you need to be within certain specifications. This requires a thorough understanding of the original product and how different bioprocesses might impact efficacy or other features of the molecule. The quality of the molecule and the time it takes to produce with a given plant capacity are critical variables. You need to understand your process and what quantity you require for your target market. You need to get the desired cell line with the right characteristics, and you need to maintain biosimilarity of the molecule through scale-up. It's also always beneficial to obtain regulatory input – especially from those overseeing your target market. Local regulators can work in different ways – both subtle and dramatic.

With biosimilars, the biggest piece of advice I can offer overall is to align yourself with someone who has experience and expertise with the inherent characteristics and sensitivities involved in bioprocessing. There is plenty of support out there that can help you get to market faster. In addition, you need a team that can analyze a molecule in detail and tell you whether it has the right quality attributes. You also need a team that can control and refine the process documentation so that it's robust and acceptable to your chosen regulators.

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By William Aryitey

# What's on the Box?

Serialization deadlines are nigh, but is the industry ready? We ask six track-and-trace gurus.

The worryingly common misperception that serialization is simply a case of "adding a label to a box" vastly underestimates the complexity of implementation, which includes in-house IT system creation, European/American regulatory data uploading, new packaging requirements, supply chain adaptation, and more.

The deadline set by the FDA for the US is November 26, 2018 (1) – delayed from November 2017 – while the EMA's EU deadline is February 9, 2019 (2). Given the scale of change required to implement serialization, there's precious little time for companies to complete the process – even with the US deadline delay. Companies – big and small – may still have queries surrounding the topic, and so to answer those questions and explore the topic in more detail, we've gathered a panel of serialization gurus.

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## The Gurus:

Christoph Krähenbühl is Senior Director at 3C Excellis Europe, and part of the Commercial and Partnership Management team at the European Medicines Verification Organization (EMVO). He was one of the original experts on the European Federation of Pharmaceutical Industries and Associations' (EFPIA's) Coding and Serialization team, and has been working on the subject since 2006.

Shabbir Dahod is the CEO of Tracelink, which has developed a track and trace network platform. He began the early part of his career looking at bleeding edge solutions which led to a senior leadership role at Microsoft. Inspired by Sanjay Sarma's MIT work on RFID and other identification platforms, Shabbir investigated the use of serial numbers to differentiate bottles, leading to his interest in understanding how it could be used to prevent pharma counterfeiting.

Eric Tjoa is the owner and CEO of Tjoapack. He started the pharmaceutical packaging company in 1989 to improve medication safety in hospitals through coding and serialization. Eric subsequently ventured into a broader range of pharmaceutical packaging services and, ever since, has had the personal goal of helping to contribute to a more efficient and safe pharma supply chain for all.

Erik Haeffler is the Vice President of Manufacturing Services and the Head of CSR at Recipharm, a contract development and manufacturing organization. He leads Recipahrm's solids and non-sterile operations in Europe, is responsible for the group's sustainability work, and is accountable for operations development across the company.

Frank Binder is the Vice President and Global Head of Supply Chain Management at Santen Pharmaceutical, a drug company specializing in ophthalmology and rheumatology medicines. Frank is in charge of logistics and supply chain projects, and has recently rolled out Santen's serialization undertaking.

Mark Davison is the founder of consulting firm Bluesphere and the author of the best seller "Pharmaceutical Anti-Counterfeiting: Combating the Real Danger from Fake Drugs". He is a biochemist by training, and spent his early career at GSK and several biotechs. Mark has spent the last eleven years in supply chain traceability and security.

## How have attitudes to serialization changed?

*Christoph Krähenbühl:* People first started seriously talking about serialization in the pharma industry around 2005, when the focus was very much on stopping fake drugs. A number of technologies were reviewed to help deter counterfeiting, with serialization being just one of the potential solutions raised. Ultimately, I believe that putting a unique serial number on each package and verifying it against a securely kept database is a powerful tool for preventing counterfeits, fraud and theft, but serialization also opens up other opportunities too, in terms of interacting with information and where it flows. In that sense, serialization is not only a tool that offers solutions to a specific problem, but one that also leads to wider opportunities. While the immediate focus needs to understandably rest on achieving compliance with regulatory requirements, visionary companies keep at least one eye on these wider opportunities.

*Shabbir Dahod:* Initially, there was a lot of resistance to implementation because serialization involves sharing data. But the regulators stressed that the industry needed to do something because counterfeits were damaging everyone, from patients to businesses. The regulators basically indicated that companies needed to work together to come up with an approach that they were satisfied with, which regulators would then evaluate based on how well it protects patients. It's taken the last 14 years for the industry to find common ground, go to regulators, and say "this is the law we want," which is why we're now seeing deadlines in place in the US and the EU. The approach and regulations around serialization will vary between different countries because everyone has to adapt based on the unique dynamics within their own markets.

*Eric Tjoa:* Historically, the pharmaceutical industry has been slow to adopt serialization. The national authorities in Belgium and Turkey were early adopters in 2004 and 2010 respectively, but any further developments have taken a long time to materialize. With the introduction of serialization legislation in the two biggest pharmaceutical markets, the US and EU, the industry is being forced to act on a grander scale and people are slowly beginning to see the benefits serialization can bring, both in terms of patient safety and supply chain management.

*Erik Haeffler:* Serialization is now widely recognized as a positive step for the pharmaceutical supply chain. Counterfeit medicines cost the industry hundreds of thousands of dollars per annum, place patient safety at risk, and have a lasting impact on a pharmaceutical company's reputation. Serialization regulations have been welcomed by most as a way to make it harder for these drugs to enter the supply chain.

## What are the key lessons learned so far?

*CK:* First of all, we have learned much about the technology itself – and some of the anticipation of how easy implementation would be has been corrected because technology is only one part of the serialization process. You've got to get the foundations right, otherwise the whole building will topple over. The other key lesson is that one size does not fit all: this is a widely diverse industry in terms of size, complexity, and area of activity so putting the right solution in place in the right way is critical. The industry as a whole has learned valuable lessons in terms of laying the foundations for this new type of infrastructure. There have been many challenges, costs, and painful moments, but now there's much learning to tap into. In the long-term, this will be seen as a positive thing since it's forcing everyone to up their game.

*Frank Binder:* There is an understanding that we all have to think beyond our own companies. We have to think along the supply chain – both upstream and downstream – and there is now more openness as an industry. We still have much to learn, and the challenges so far have been difficult to overcome, partly because authority requirements have changed. For example, there have been false starts in the US, with companies investing in RFID technology and adhering to California requirements, before they were both superseded. Such false starts have made it difficult for companies to trust serialization. Pharma companies like to "wait and see" before investing. The danger with that strategy is that by the time you realize you have to invest, you don't have much time left.

*ET:* I agree with Christoph – the most common misconception is that serialization is a "simple" process, despite the experience the industry already has. There is a huge amount to consider, from hardware and software requirements to the right data management solutions, which ultimately lead to new business processes. It's important that serialization becomes integrated throughout a company's supply network to avoid unnecessary handling steps or reworking.

*Mark Davison:* The industry is learning that serialization is more difficult than it looks, and takes longer than you expect. Although the codes are applied with relatively simple technology, such as inkjet printers, there are fundamental shifts in data management, system validation, and quality processes that affect the whole company and constitute a major change program, as well as a new business risk.

## What are the biggest challenges in implementing serialization?

*CK:* Many consider serialization to be just an engineering project, but every part of a company is involved. Serialization is

## Examples of Track and Trace Around the World

- June 2010 – Turkey – Pharmaceutical Track & Trace System introduced
- July 2011 – European Union – EU adopts the Falsified Medicines Directive
- October 2011 – India – Exporters required to print barcodes on tertiary drug packaging
- October 2013 – India – Secondary level packaging must be serialized
- November 2013 – USA – Drug Quality and Security Act signed into law
- July 2014 – Nigeria – Implementation of Mobile Authentication Services for anti-malarial and antibiotic medicines
- January 2015 – South Korea – Unique serialization according to GS1 standards
- March 2015 – Saudi Arabia – Outer packaging must contain human-readable serialization and Data Matrix symbol
- August 2015 – Argentina – Every saleable unit must be serialized
- December 2015 – China – Unit, bundle, case, and pallet must be serialized with a government-issued number; aggregation is a regulatory requirement
- January 2016 – South Korea – Serialization mandatory for all product at secondary packaging level; serialization at tertiary level encouraged
- March 2016 – India – Uniquely serialize pallets, cases, and saleable units
- September 2016 – Australia – Barcodes and enhanced labeling required (not serialization)
- March 2017 – Saudi Arabia – Unique serial numbers required for all prescription drugs
- January 2017 – Australia – Serialization required for hemophilia products
- November 26, 2018 – USA – Deadline for DSCSA serialization requirements
- February 9, 2019 – European Union – Deadline for FMD serialization requirements

*"The industry is learning that serialization is more difficult than it looks, and takes longer than you expect."*

as big as an enterprise resource planning (ERP) project – potentially bigger. It involves many different processes and pathways, and we must recognize that people's understanding of what's needed and why, is more limited in different parts of the organization. Getting the whole organization involved and keeping it involved is actually quite a challenge. You need to get your senior stakeholders on board – and then you need to keep them on board! In some companies, we still see an element of denial or wishful thinking around what may or may not happen regarding serialization requirements; it's important for companies to be clear in understanding what they need to do and to articulate that knowledge very clearly internally – and also externally to their trading partners.

Another misconception is that there will be a lot of information available to all parts of the industry but, in reality, the amount of shared information available is very limited – at least in a European context – for legal reasons and privacy concerns about how the information is used and how it impacts other business stakeholders. Again, I expect this will change over time, but for the immediate future we'll see serialization being focused on a narrow compliance angle.

*FB:* I think that there is a significant challenge for small companies in particular. Small companies don't have the same dedicated resources to put into serialization as a big pharma company, but they still have to follow the same process: set up a strategy, set up the processes internally, connect to a contract manufacturer or handle manufacturing internally, and then join up with logistics partners to comply with each market's requirements. Small teams – like my own team at Santen Pharmaceuticals – have to be clever and efficient.

*ET:* The guidelines are fairly clear; however, there has been a huge amount of concern surrounding the cost of implementing serialization across manufacturing and packaging lines. As Frank says, serialization is challenging for small companies – the upfront investment required to comply with regulations is simply unachievable for some, and for others there is a growing belief that serializing for markets that bring in less revenue is no longer worth it. I think that the industry could benefit from more guidance on how to better manage these concerns.

*MD:* Companies often run into problems because of the slight variations in regulations between countries. Although the data requirements may be broadly similar, the local nuances require separate setup procedures. Keeping track of these legal idiosyncrasies is time-consuming. There are also issues of data compatibility between different serialization systems, from production line equipment to reporting software, although these are largely being addressed by interoperability initiatives within the industry.

*EH:* I see data as the biggest challenge. Serialization involves the creation, management and storage of a huge amount of data. It is vital that companies have a suitable system in place to manage data – such as cloud storage. Without this, a serialization solution is simply not fit for purpose.

## Whose responsibility is it to ensure that products are serialized?

*MD:* The responsibility typically lies with the Marketing Authorization Holder (MAH). Some aspects of the task (such as code printing) can be delegated to contract development and manufacturing organizations (CDMOs) for example, but the ultimate responsibility for the generation and reporting of accurate data lies with the MAH. This means that even tiny, virtual MAHs need validated software and processes to manage that new responsibility.

*EH:* It is vital that CDMOs recognize their responsibility as part of the supply chain. Accountability falls onto every company involved in the supply chain to ensure they give serialization the attention it deserves. Many pharmaceutical companies work with multiple contract partners, and supply to multiple markets with various serialization requirements, adding a huge amount of complexity. CDMOs will be vital in ensuring that the new requirements are implemented successfully.

*FB:* The cost burden will fall on MAHs. In the end, CDMOs will charge out everything – and with a margin because that is their business model. MAHs will also have to pay for all verification system implementation.

## Is the industry prepared for the upcoming deadlines?

*CK:* The constraints on data quality are very high. With every customer we've worked with, we often find they have a lot of homework left to do, like the fact that their product master data may not include the product codes that are now part of

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## Anti-Counterfeiting Action

*Track and trace is now mandated by most regulators, but there are also other technologies that can help combat counterfeiting.*

- Radio frequency identification (RFID) uses an electronic tag to store data that can be read or retrieved using a radio frequency-capable device. RFID tags containing batch or individual pack information can be attached to packages, available to scan for verification.
- Tamper-resistant packaging is common on most drugs today. Blister packs, seals and film wrappers, for example, provide visible evidence that a product may have been tampered with. This will be required by the EU as part of their FMD Another approach that can be incorporated into the packaging is an optically variable device (OVD), which is an image that shifts color or pattern when light strikes it at different angles. This image can house security elements and patterns and is difficult to forge. Many companies also place covert markers on packaging.
- One anti-counterfeiting approach that goes deeper than primary packaging is to use physical chemical identifiers (PCIDs), a group of substances including inks, pigments, and taggants integrated into pharmaceuticals, such as tablets, for verifying authenticity. Inert, edible taggants can be customized and added to a drug excipient or coating, allowing identification of authenticity at a per-pill level.
- Analytical techniques, such as raman spectroscopy, can be used to create a "fingerprint" of a drug. Most often this is done in laboratory tests, but portable instruments have now been developed that can scan a drug – in some cases through sealed packaging – to check if it is counterfeit.
- Some countries exploit the prevalence of mobile phones to help combat fake drugs. In Nigeria, fake drugs are a big problem. Similar to serialization, a unique code is placed on each packet. The patient or healthcare provider then texts the code to a specific number – and quickly receives an automated response stating whether the medicine is real or fake.

the pre-printed artwork. If artwork or packaging design cannot accommodate a Data Matrix and an anti-tampering device, then you need to do a major rework. And this is all work that is beyond the narrow scope of the serialization system implementation that is typically seen as the immediate priority All of this amounts to long lead times, and many companies have trouble getting their head around what the full program scope includes, as well as how to get it up and running.

*FB:* Some companies are prepared, others are not. When saddled with extra manufacturing costs at CDMOs and the extra costs of maintaining the verification systems, some products with already low margins might be at risk. It doesn't need to be a huge cost – even a few cents added to the cost of goods could make certain products unviable.

*MD:* Frank mentioned earlier that serialization was a challenge for small companies in particular, and he is correct. Most of the major drug companies have invested heavily to make sure they will be compliant for the appropriate deadlines in the geographies in which they operate. Small and mid-size companies with fewer resources, however, are typically much further behind – and I expect that some will not be compliant. Some virtual companies with no in-house manufacturing may also be forgetting their responsibilities – they will still require some software and new processes. There are various mandatory reporting tasks that cannot be delegated. I also find that there is a separate issue around pharmacies, which are expected to verify the codes under the EU Falsified Medicines Directive (FMD).

From what I've seen, pharmacy readiness is potentially as big a concern as manufacturer compliance.

*EH:* Companies are preparing for serialization in a variety of ways, but there is no industry standard, given that markets have different requirements. Recent polls held at the NEXUS 17 serialization conference showed that the overwhelming majority of pharmaceutical companies, CDMOs, contract packaging organizations, and third-party logistics providers aren't ready. Companies have underestimated the extent of serialization thus far, but have a bit of breathing room through the extended deadline in the US. The additional time should be used to implement a stringent solution that is fit-for-purpose – and companies can also take the opportunity to examine how data sharing might improve other business efficiencies.

Even with the US deadline extension, it's still fairly late to start considering a solution and begin the implementation process from scratch – the European Stakeholder Model (ESM) suggests that four to five years is a realistic timeframe for implementing serialization. Companies without a solution in place need to start developing a strategy now.

### How will serialization affect counterfeiting?

*CK:* Serialization is not a perfect solution, but there is no perfect solution. It is always a trade-off between the cost and complexity of the countermeasures you put in place, versus the effect they will have. Serialization means that, in a pharmacy context for example, the checkout will be very secure. In the

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*"You've got to get the foundations right, otherwise the whole building will topple over."*

past, there have been incidents where counterfeit products have been detected in the legal supply chain, but with serialization these products cannot be dispensed to patients. Trading online, of course, is a different case and I think part of solving that lies with trading partners, or pharma companies themselves being more open. The serialization information companies upload to the EU system could be made accessible to patients or medical professionals. For example, smartphones could be used to scan and verify a package to make sure a real product has been received. This is not part of the 2019 EU FMD's scope of course, I want to be very clear about that. But it is inconceivable that the infrastructure that is now being put into place at significant cost will not be used to deliver more tangible patient safety and other benefits, over time.

*SD:* Talk to any brand owner and they'll tell you that seven percent of their inventory is probably counterfeit – and that's the average. In some markets it can be up to thirty percent. Ultimately, serialization is about getting integrity in the supply chain. The supply chain is crucial for the pharma industry and we need to keep raising the bar. Pervasive implementation of serialization will make products more traceable and we should see the number of counterfeits reduce in the future. The main reason that counterfeiters exist is because they remain hidden – once something is in the supply chain it's hard to find who put it there. As soon as you can trace a product more easily, it won't be a good business for counterfeiters and criminals to be in.

## What will be the long-term effects of serialization on industry?

*CK:* In the short-term the industry will take a hit, there's no doubt about that – after all, serialization involves considerable investment. Companies will also find that serialization has an initial impact on their overall line efficiency and effectiveness, so the outputs will dip before they recover again. However, even in the short-term, there can be a benefit, as implementing serialization also forces companies to "shape-up" their processes. But some companies unfortunately won't be able to shape-up. I have talked with many stakeholders about the challenge of serialization and everyone has a sense that it will lead to consolidation. On the other hand, this creates opportunities in the short-term for the companies that have got their act together early on, and puts them – and the rest of the industry – in a position where they will be able to reach the bigger benefits alluded to before.

*SD:* There are certainly challenges ahead and some companies will find serialization difficult, but serialization is also an opportunity for improvement, particularly in terms of marrying information together. The information network and operational handling will continue to mature, and the lessons we learn will shape future regulations. The industry will also be able to use data from serialization to achieve more efficient outcomes and better performance all the way from manufacturer down to pharmacist. At the moment, serialization efforts are about compliance, but soon it will move from compliance to good business practice.

*ET:* Eventually, the industry will be able to use serialization to increase supply chain security and realize logistical improvements. Full visibility of the product throughout its lifecycle will allow everyone involved in the supply chain to access product information and perform checks. Beyond verifying medicines, the improved exchange and processing of data will connect the whole supply chain from manufacturer to patient. Companies will be able to look at legacy data over time and optimize their logistics operations through real-time monitoring. The result? Accurate demand planning as opposed to assumption-based forecasting, improved warehouse management, shipment visibility, and more efficient distribution.

*MD:* My colleagues and I are optimistic that serialization will be an enabler for other benefits related to digital health. For instance, the transition to individual pack identity is an important milestone on the road to fully personalized medicine. The full value will probably not be felt for some years, but in the meantime serialization will help address supply chain vulnerabilities and improve pharmaceutical security.

*EH:* I agree with Eric. In the long term, we can look forward to a highly secure supply chain where falsified medicines are filtered out before they ever reach the patient because of end-to-end visibility. The industry will also see additional business benefits, such as faster information sharing, cost effective and accelerated integration throughout the supply chain, and improved quality practices. If companies can seize the opportunities that serialization offers, then there is undoubtedly value beyond compliance.


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## Regulations Explained

- The Drug Quality and Security Act (DQSA) was enacted by Congress on November 27, 2013. Title II of DQSA, the Drug Supply Chain Security Act (DSCSA), outlines requirements for an "electronic, interoperable system" that can track certain prescription drugs as they are distributed throughout the country.
- The law mandates product tracing, product verification and serialization – this applies to drug manufacturers, repackagers, wholesale distributors, dispensers, and third-party logistics providers.
- The aim is to help keep potentially dangerous counterfeit or falsified medicines out of the legitimate supply chain with a unified system across the country – previously, different states had different approaches to tracking drug products.
- Manufacturers need to affix or imprint a product identifier to each drug package – comprising a product's lot number, expiration date, national drug code and a serial number.
- The tracking system must enable transaction information, transaction history and transaction statement.
- Repackagers will be expected to serialize products by November 27, 2018; distributor traceability is required by November 27, 2019; and dispenser traceability is required by November 27, 2020. Full unit-level traceability must be implemented by 2023.

*Further information: FDA, "Drug Supply Chain Security Act (DSCSA)", (2017). Available at: http://bit.ly/2tIy0b2.*

- The EMA's rules for serialization fall under the agency's Falsified Medicines Directive (FMD), which was introduced in 2011 to help fight falsified medicines.
- Drug manufacturers are required to add safety features, a unique identifier carried by a 2D barcode and an anti-tampering device on the packing of prescription and certain non-prescription medicines by February 9, 2019.
- The 2D barcode must include the serial number, national reimbursement number (if requested by a country), the batch number, and expiry date.
- Medicines will be verified at point of supply to the public, using an end-to-end verification system. While medicines at a higher risk of falsification should also be checked at the wholesaler point of supply.
- The IT systems with verification information should be set up and managed by medicine stakeholders, and national authorities should have access to these repositories.
- Medicines in Europe are usually packaged and sold at the unit of use level, whereas in the US medicines may be bulk packaged. This means that the volumes of products to be serialized in the EU is expected to be several orders of magnitude greater than in the US.
- Each member state will have the flexibility to add their own serialization requirements.

*Further information: EMA, "Falsified medicines", (2017). Available at: http://bit.ly/1JQqf28.*

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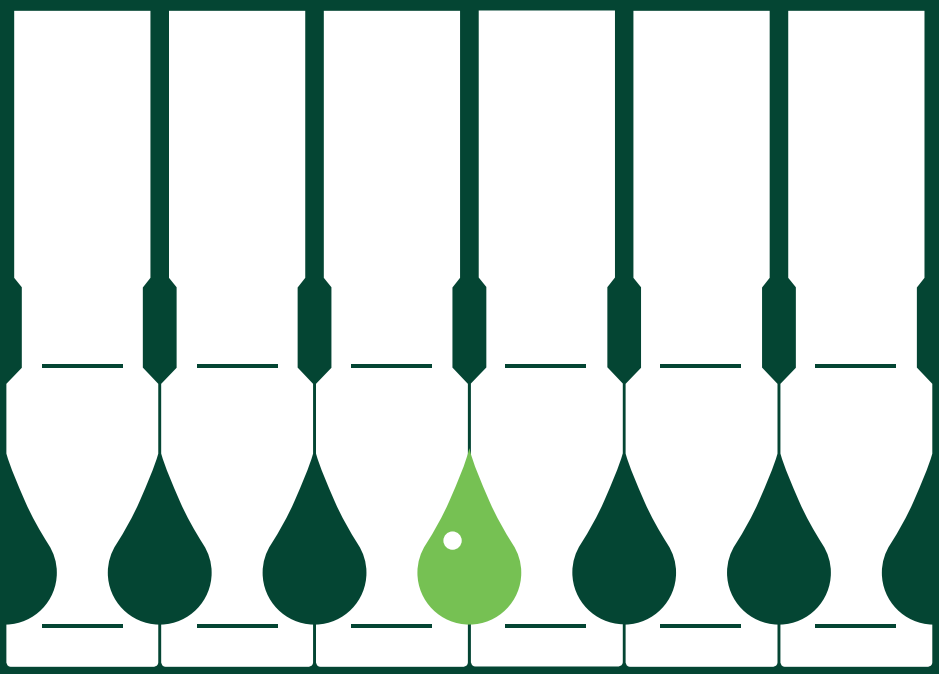

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# The Small-Molecule Problem Solver

**Today's small molecules are increasingly complex, but generic producers must keep track of the trends – since today's innovator drugs are tomorrow's generic targets.**

Having worked with generic drugs since the 1990s, Paul Evans, Vice President and General Manager at Johnson Matthey, has seen the industry go through many changes. Today, small molecules are becoming more sophisticated, posing challenges to both innovators and generics manufacturers alike. Four years ago, Evans joined Johnson Matthey, tasked with the aim of creating additional value for the company by finding innovative ways to expand the generic API portfolio – and he believes that jumping in at the deep end and lending a hand in product development is key.

### What are the main challenges with today's small molecules?

Scientists now have a good understanding of how biological processes work, leading to more complex and efficacious medicines. Today's small molecules are increasingly potent and targeted, and can involve challenging chemistries or handling procedures that companies may not want to – or may be unable to – do themselves, especially when it comes to moving from the small scale to the larger scale. Sophisticated molecules can also pose challenges to formulators, particularly as drug substance and drug product are traditionally viewed as quite separate areas – usually, the API is developed and then samples sent over to formulators to solve issues with bioequivalence and bioavailability in a trial and error approach. A far better method would be to collaborate at the intersection.

Generic manufacturers have to follow the trends that are happening in the originator space and be prepared to deal with complex molecules, since today's originator molecules are future targets for the generics industry. The difference for the generics space is twofold: speed to market and navigating the intellectual property landscape. To achieve these targets, you have to bring your own development skills and technology to bear.

### Why is differentiation in the marketplace so important for generics?

Generic molecules are by definition the same, but manufacturers can differentiate through manufacturing processes, intellectual property and creative business models. Good chemistry skillsets are important because you need the ability to dive into the physical properties of products, such as how they are formulated and how they perform in the body, and technical expertise to identify intellectual property opportunities. Of course, generics companies know that differentiation is important but in reality it's difficult to achieve. It is also a difficult field to collaborate in because collaborations involve trust, which takes time to build – and time isn't always available when you are rushing to get to market.

### How is Johnson Matthey adapting to changing industry needs?

Johnson Matthey is over 200 years old, but to get to our next centenary it is important to adapt. We have been making APIs since the 1970s, but with small molecules and drug development becoming more challenging, we started to ask what more we could do for our customers. And the answer was collaboration. When you are in the API business, you accumulate a lot of technical capability and chemistry skills that can be applied to a wide portfolio of products. We came up with the idea of investing and developing generic products in collaboration with our customers, believing that the sharing of risks would be very valuable. Most generics companies seek a large portfolio of products but their R&D teams can only do so much. With our model, the two teams work together collaboratively to find the best overall solution for the API and drug product, which allows for a quality-by-design led approach to development. For example, using particle science and upfront characterization provides a better understanding of how an API is going to work in the formulation – and the drug substance can then be tailored to help the formulator reach their target faster, and with a more sophisticated design space. Collaboration can really help accelerate development times – a valuable edge given that speed to market is key with generics.

Collaboration is not just important with our customers, but with other companies who have technology that we don't, and who can potentially make a difference. In June of this year, we announced our collaboration with Intrexon. Intrexon is an expert in the engineering and industrialization of biology and we will be working to use its technologies to help with the production of peptide-based APIs.

### Any final tips for small molecule success?

The technical toolbox is incredibly important. It's common to find experts in a specific technology, but the danger is that they will try to force fit that technology to solve all problems. In my view, it is far better to look at a range of solutions and to examine which ones provide the best outcomes. The synthetic pathway can greatly influence how you purify and isolate the product, so your chemistry approach influences your solid form and can impact yield, cycle time, and further processing requirements. Marry these technical capabilities with a collaborative approach and I feel you have a powerful combination.

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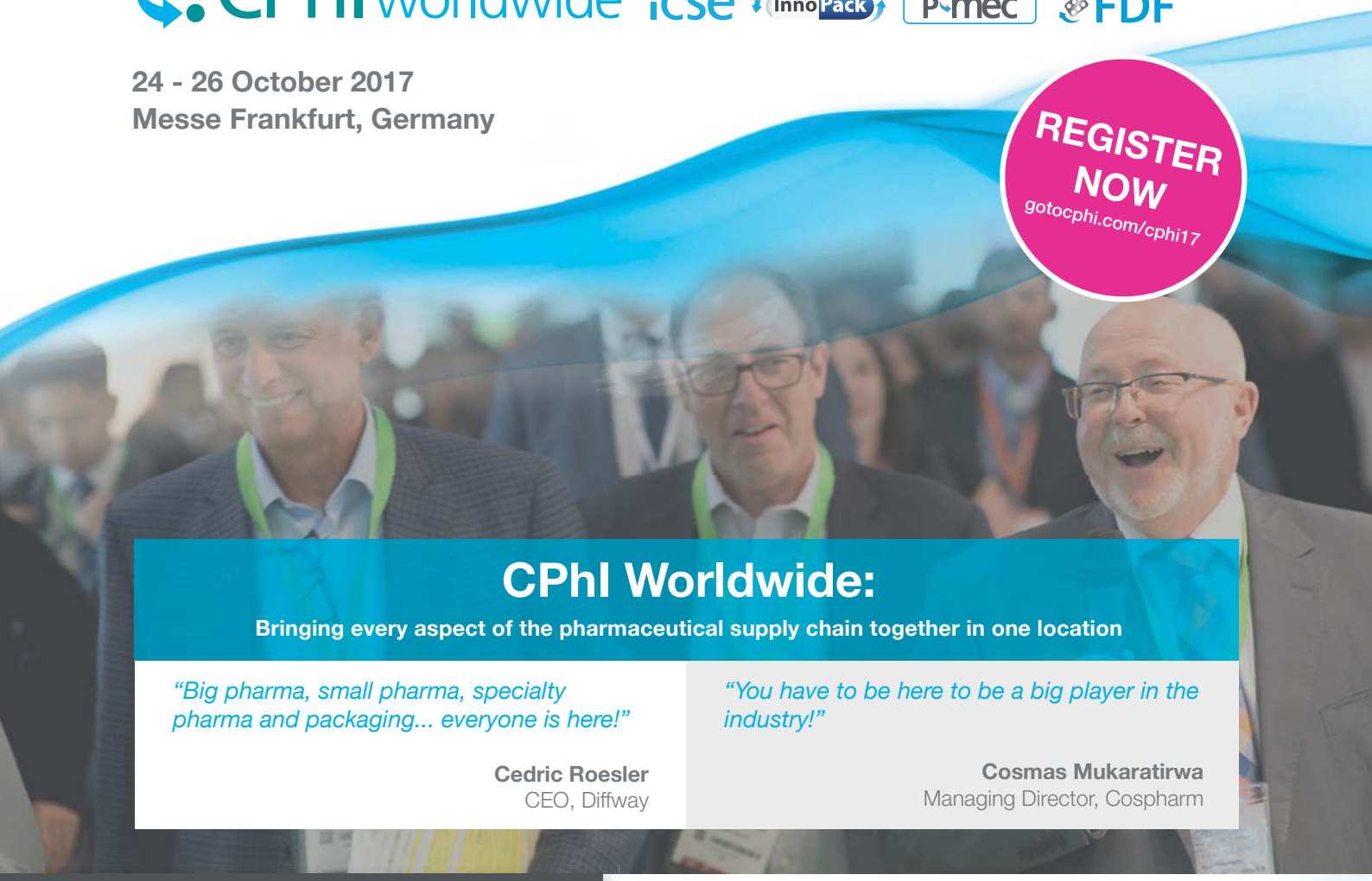

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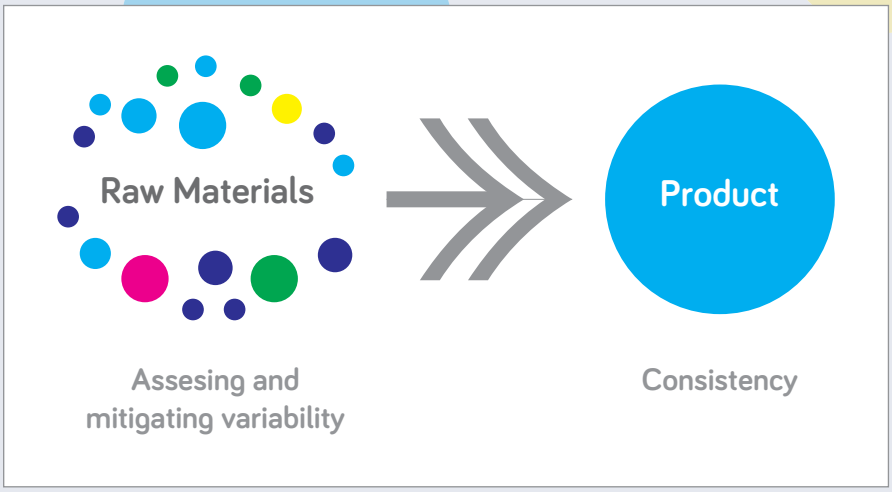
# Know Thy Raw Materials

**We asked customers what they wanted from their cell culture media suppliers and the reply was, "understand your raw materials". So nine years ago we set out to characterize and evaluate our raw materials – this is what we found...**

*By Chandana Sharma, PhD*




From our perspective as a cell culture media supplier, there are hundreds of possible raw materials which could be in a formula, including amino acids, vitamins, fatty acids, and salts, many with multiple functional groups. Raw materials can come from any number of possible sources, and even the same ingredient from multiple sources. Some raw materials are very well defined and others may lack a complete profile. Understanding raw material differences has become vitally more important to companies like ours. Our customers strive to understand variability and the impact on their biomanufacturing process, they look to improve their cost to manufacture and reduce risk to the patient. So they look to us to know more about our raw materials. This is exactly what our customers told us in late 2008 when we carried out a survey asking what they expected from cell culture media suppliers – the clear message was that a thorough understanding of raw materials and potential variability was crucial. And so Merck KGaA set out on an ambitious program of raw material characterization and evaluation.

At the time, Merck KGaA was focused heavily on developing cell culture medium rather than its building blocks, so we had to take a step back and decide on a strategy. Variability in cell culture raw material is, of course, inevitable, but too much variability can impact the overall performance of the culture medium, bioprocessing parameters and the process output. A cell culture media can consist of 70 to 100 different raw materials and the variability is cumulative, so it needs to be controlled within reason. A good understanding of the raw materials and variability builds a good picture of the medium as a whole and its performance.

*"Our data can also be used to advise customers on the most suitable cell culture medium."*

## A question of variability

The first question for our characterization program was, what should we study? With hundreds of raw materials in our inventory, we had to pick and choose, so we performed a risk assessment to identify "high risk raw materials." From this we created a prioritized list of raw materials. We then undertook an orthogonal approach to characterize those materials, which included chemical and biological assessment. Chemical assessment was focused on understanding the impurity profile, whereas biological characterization was focused on understanding the impact of impurities or variability on cell culture processes.

Using the right tools and techniques for the study was vital to get the best data, which meant investing time and resources into approaches such as mass spectrometry, liquid and gas chromatography, and multivariate data analysis tools. On the biological characterization side, we developed high-throughput biological assays and markers. We took a dose-response approach and studied raw materials in multiple cell lines. There have been some remarkable advances in the sensitivity of analytical instrumentation in recent years, which allowed us to carry out elemental analysis at the parts per billion scale. Overall, we produced a tremendous amount of data and learned what variability was normal and acceptable for our raw materials, and what was not.

### Understanding your partners

One aspect of our raw material characterization program was to study and understand the inter- and intra-lot variability of a given supplier. We had in excess of one hundred different raw materials, but for each of those we also had two to three suppliers (it's always advisable to have some redundancy in the supply chain and not be dependent on one supplier). If, for example, we had L-Lysine coming from supplier A, we had to understand the variability within supplier A, as well as suppliers B and C. Overall, we had to understand how each supply of L-Lysine might differ, and then examine how the variability could be minimized.

We also realized the importance of integrating the characterization program with our quality systems to proactively prevent any variability in raw material from impacting the quality of the final product. Today, we have a two tiered approach of screening changes in the raw material supply. We also have very good relationships with our suppliers and discussed our findings with them. For example, if there was a problem with a certain raw material then we collaborated with the supplier on how we could overcome this.

### Knowledge is power

The most important finding was that our raw materials were relatively pure, especially the defined small molecules, which was a relief! When we did see variability, it was coming from trace metal salts or undefined raw materials like hydrolysates. The trace metals finding was surprising because it was not an initial focus of our study. This changed with the results and we ended up diving deeper into the topic of elemental impurities, particularly because it was so important for certain inorganic salts like sodium chloride. In time, we expanded elemental impurity testing to all major raw material groups, including amino acids, vitamins and more.

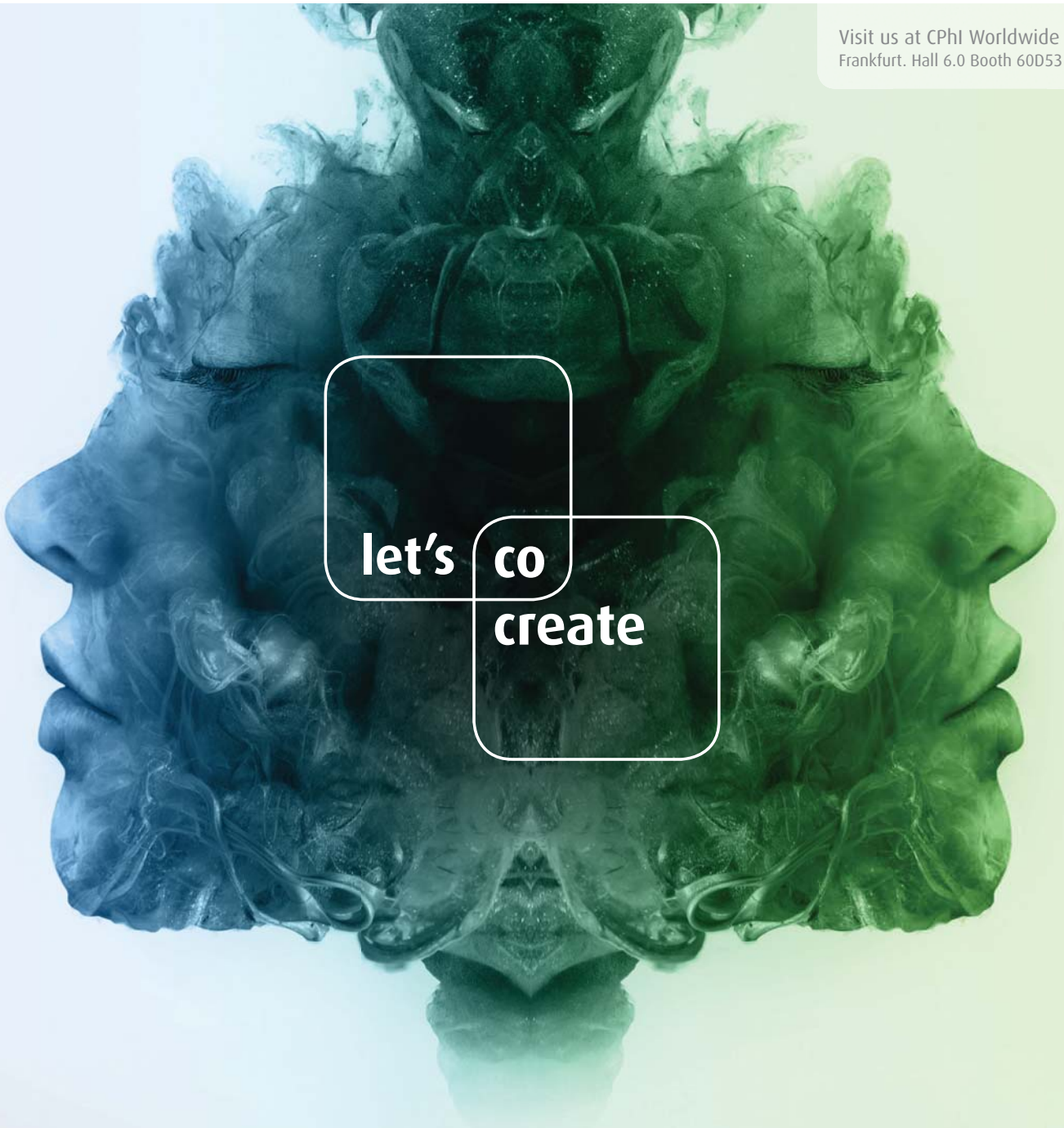
*"The most important finding was that our raw materials were relatively pure."*

There will always be some variability in raw materials – since some of our raw materials are byproducts of other processes, and we may not even be the primary industry for it. We have taken steps to ensure that our suppliers are safe, but we need to appreciate that we are one of many customers so we also need to have mitigation and quality control procedures at our end. For example, we learned less than a 1 percent impurity in poloxamer 188 had a huge impact on cell culture processes, and have such developed a quality control cell assay to detect and prevent entry into our supply chain. Thanks to our detailed study, we now have a great deal of information about our raw materials and the impact on cell culture. Information is never a bad thing – you may not choose to act on it, but it allows you to make informed decisions. Many of our customers have used the data we provide about our cell cultures to make changes to their formulations. For example, they may already know there will be a specific amount of manganese or copper as background impurity, so they can tweak their formulations or processes if necessary to account for the variability. Our data can also be used to advise on the most suitable cell culture medium for a given product. A biopharma company may require a cell culture medium with a certain amount of iron, but may have a product that is sensitive to zinc. Now that we have characterized the impurities contained within our raw materials, we

can advise our customer that one of our raw materials, ferric citrate for instance, contains zinc. The customer might then ask what other sources of iron are available, to which ferric ammonium citrate might be the answer. We can then supply a cell culture medium that is tailored to the specific needs of the customer. I have seen many success stories where we have collaborated with our customers to overcome problems – all products are different and cell culture systems can be customized. Because of this, deep collaboration with suppliers is crucial. This is true for us with our suppliers, and also our customers.

Overall, the painstaking process of characterizing our raw materials and figuring out how they impact biological systems and our cell cultures has allowed us to be more transparent with our customers. It seemed like quite the task when we first embarked on the project almost a decade ago, but the hard work is now paying off in terms of deepening our relationships with customers and suppliers – securing the supply chain from top to bottom.

*Chandana Sharma, PhD, is Head of Cell Culture Raw Materials, Upstream R&D, at Merck KGaA.*

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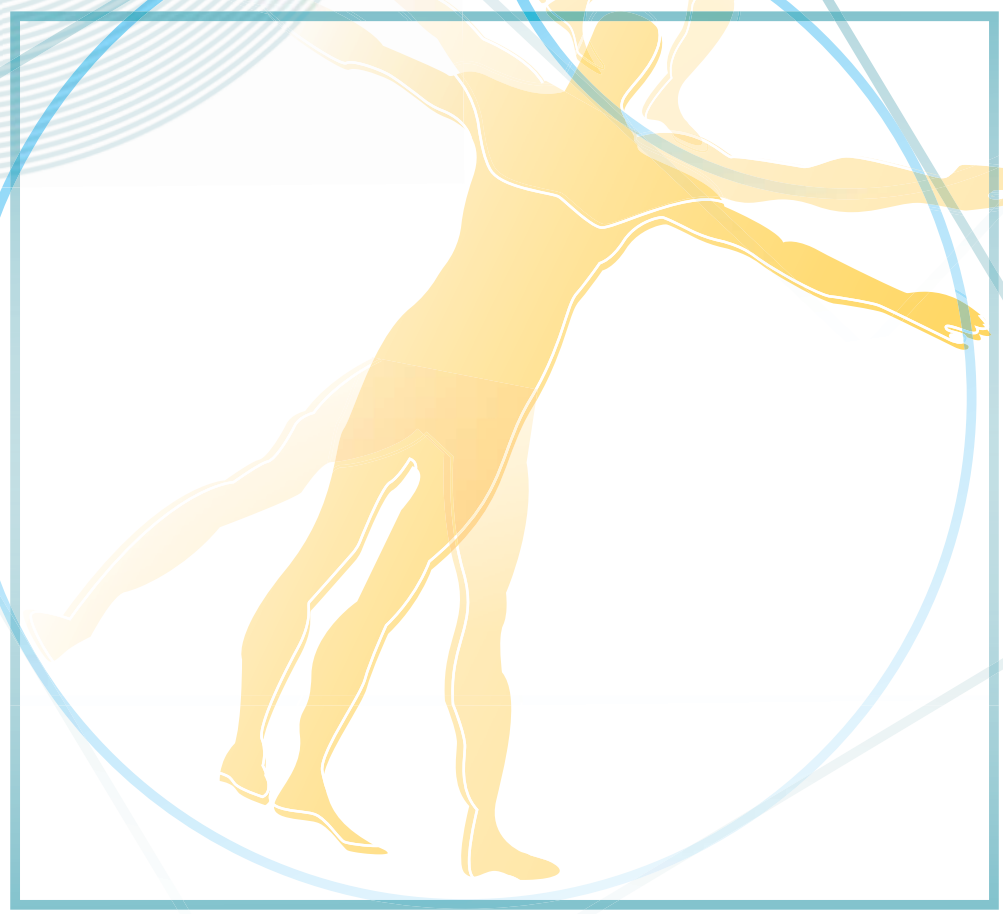
# Twenty-First Century Cell Therapy

**Advanced medicines are full of promise, but also pitfalls – not least making sure that manufacturing costs don't trump the reimbursement price.**

*By Denis Bedoret*



In August, The Medicine Maker's advanced medicines supplement illustrated the explosive growth of the cell therapy industry (1). Over the last decade, the industry has moved from great expectations to clinical realities, with a growing number of ongoing clinical trials in multiple indications. Clinical trials are now primarily sponsored and driven by industry, rather than academia – an exciting feature of the maturing field. There is also growing acceptance that allogeneic products will not completely replace autologous transplantation approaches – there will be a need for both systems. As more autologous therapies come to market, the industry is also getting to grips with the supply chain and business model challenges.

Initially, approved cell therapy products tended to be focused on regenerative medicine and tissue engineering, but now the field has shifted to immunotherapy. Novartis' CAR-T therapy, Kymriah, will hit the market soon, after being approved by the FDA at the end of August. It will be manufactured for each individual patient using their own cells and cryopreserved to allow for treatment flexibility. Other companies are also hoping for CAR-T approvals; for example, Kite Pharma won the 2017 "Clinical Trial Result of the Year" for its Pivotal CAR-T Trial in Patients with Aggressive Non-Hodgkin Lymphoma at the Clinical and Research Excellence Awards. It's safe to say that immunotherapy and cell therapies are in the spotlight.

Although cell therapy knowledge and expertise has increased significantly over the last decade, manufacture still remains a challenge. First of all, it has taken time for the regulatory environment to develop, with trailblazers like Dendreon and TiGenix helping to forge the way forward. Novartis – the first of big pharma to launch a cell therapy product – will also be a key company to watch.

In terms of development and manufacturing technologies, there are a number of fundamental gaps, such as lack of processes for efficiently differentiating stem cells – not only adult mesenchymal stem cells, but also now embryonic stem cells and pancreatic stellate cells – into functional, therapeutically-relevant cell types. Similarly, there remains a pressing need for technology that can promote integration of stem cell products into three-dimensional structural matrices in the body. Looking at the manufacture of cell therapies more generally, there is a great need for more automated and closed systems (especially as human error or contamination can be fatal) – and great opportunities for equipment manufacturers to step up and cement an early place in the market.

But perhaps one of the most significant challenges in the maturing cell therapy field is getting the balance right: on one

hand you need to get to the clinic as quickly as possible, on the other hand, you need to take the time to develop a robust, efficient and commercially sustainable manufacturing process – and with a third hand, you need to ensure you have reasonable cost of goods (COGs). Many companies talk about COGs, but examples of true process optimization are rare. Going to the commercial stage with an inefficient process can result in manufacturing unit costs that exceed the realistic price of the final therapy – potentially killing the business.

## Cell mates

Given the challenges, many cell therapy medicine makers consider outsourcing – and increasing numbers of service providers are emerging. Partnerships between a CDMO and pharma companies lead to a virtuous circle: by gathering expertise from multiple client projects, CDMOs become increasingly skilled – subsequently becoming better versed at helping the industry overcome the manufacturing challenges of cell therapies.

One of the key benefits of outsourcing to a CDMO is improved cost control. The alternative (in-house manufacturing) requires enormous upfront investment, which can have a devastating impact on a company's cash situation. For example, the debt taken on by Provenge to build an in-house production facility severely hampered subsequent product commercialization efforts. Part of the problem associated with in-house manufacturing by the innovator company is that decisions regarding systems and processes must be made at an early stage – that is, without knowledge either of future needs or of the capabilities that will be required to meet those needs. Consequently, companies may find that their facilities and staff remain unutilized for long periods, such as between clinical study phases, or that their facilities and processes are not flexible enough to meet the needs of an evolving pipeline. A CDMO can also help with local manufacturing, as many large CDMOs have a global network. Given the logistics and shelf life constraints of most cell therapy products, the ability to manufacture as close to the point of care as possible can be crucial.

Although partnering with a CDMO can be an effective and less risky approach than going it alone, some companies are wary because of the perceived lack of control. In addition, finding the right CDMO is often trickier than you imagine, particularly with more and more springing up. Take your time to find the right partner, don't underestimate the technology transfer phase (crucial if you want to ensure the process is fully controlled), and be wary of any company that sees quality as a burden. It takes time to get cell therapies right, and companies should never compromise the quality and safety of products,

*"Marketing is likely to be particularly critical for revolutionary treatments."*

no matter the pressure on cost or timing.

It is important to remember that using a CDMO does not mean you have to outsource the entire manufacturing process. Some companies prefer to seek support for specific aspects, such as product characterization or the development of quality control assays that don't use up vast quantities of product.

## Future sales, future cells

COGs and reimbursement levels are key to the commercial viability of the product, and all cell therapy companies should pay close attention to these areas at an early stage. No matter how good a product is, it stands that if it is unaffordable, it will not sell. Unfortunately, prediction of price levels, which are necessary to assess whether manufacturing costs are acceptable, remains difficult given that so few cell therapies have reached the market.

Existing points of reference for cartilage products show a price of around US $20,000-30,000, while intravenously administered cell therapy products are commonly in the $100,000-200,000 range. The $665,000 price tag achieved by GlaxoSmithKline for Strimvelis, their ex-vivo stem cell gene therapy developed to treat patients suffering from a rare disease called ADA-SCID (severe combined immunodeficiency due to adenosine deaminase deficiency) cannot be seen as a benchmark given the very limited size of the market. For therapies that extend life rather than offering a cure, it is not uncommon to see chemotherapies priced at $17,000, or kinase inhibitors priced at $95,000; very often, such therapies only prolong patient life by a year or two. For therapies that can potentially save lives, reimbursement of at least $150,000 would seem reasonable. Novartis' Kymriah will hit the US market at $475,000 – less than some analysts expected.

Reimbursement levels tend to be calculated based on health economics and, increasingly, we are seeing conditional approval and pricing – at least in Europe, Japan or South Korea, where reimbursement depends on the observed level of benefits. Products that offer only a subtle improvement versus existing therapies are problematic with this model, but cell therapy products, where the benefits are usually anticipated to be significant, are a somewhat safer bet. Even so, market success is not assured; for example, Novartis' Entresto, once expected to be a blockbuster, had a slow start because of barriers to patient access and an underfunded launch. Marketing is likely to be particularly critical for revolutionary treatments – administering cell therapies is very different from traditional drugs, and effective promotion will be crucial to generate adoption by physicians and patients.

With the industry getting to grips with cell therapy manufacture, CDMOs taking the strain, and more clarity over pricing and reimbursement emerging, I anticipate a bright future for the cell therapy market. But companies – and investors – need to do the right thing if they want the right results. It is essential for companies to enter the development process with a deep knowledge of the cell product and its mode(s) of action. Analytical processes should be available from the start, and all data from early bench work and onwards should be stored and curated. Even so, additional development will be required at the Phase III and commercialization stages. Finally, I urge companies not to neglect the process optimization required to control COGs.

I am now more excited than ever before about the cell therapy industry. I feel like I am helping to write one of the most exciting pages in the pharma history book. And there are even more exciting opportunities to come; for example, development of combination therapies comprising cell products and conventional biologics. I firmly believe that the dream of curing cancer has never been so close to reality.

*Denis Bedoret is Managing Director at Masthercell, Belgium.*

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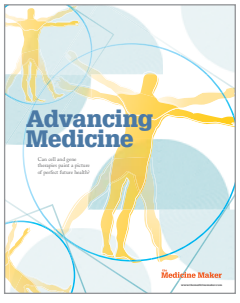


*The Medicine Maker's special report "Advancing Medicine" features insight and opinions on the rapid rise of advanced medicines and the challenges surrounding their manufacture. Topics include tackling the rise of unapproved cell therapies in the US, how to cope with the complexities of the supply chain for advanced medicines, a technical roundtable discussing the field's success stories and needs for the future, and a one-on-one interview with Steve Oh from the Bioprocessing Technology Institute at the Agency for Science, Technology and Research (A*STAR).*

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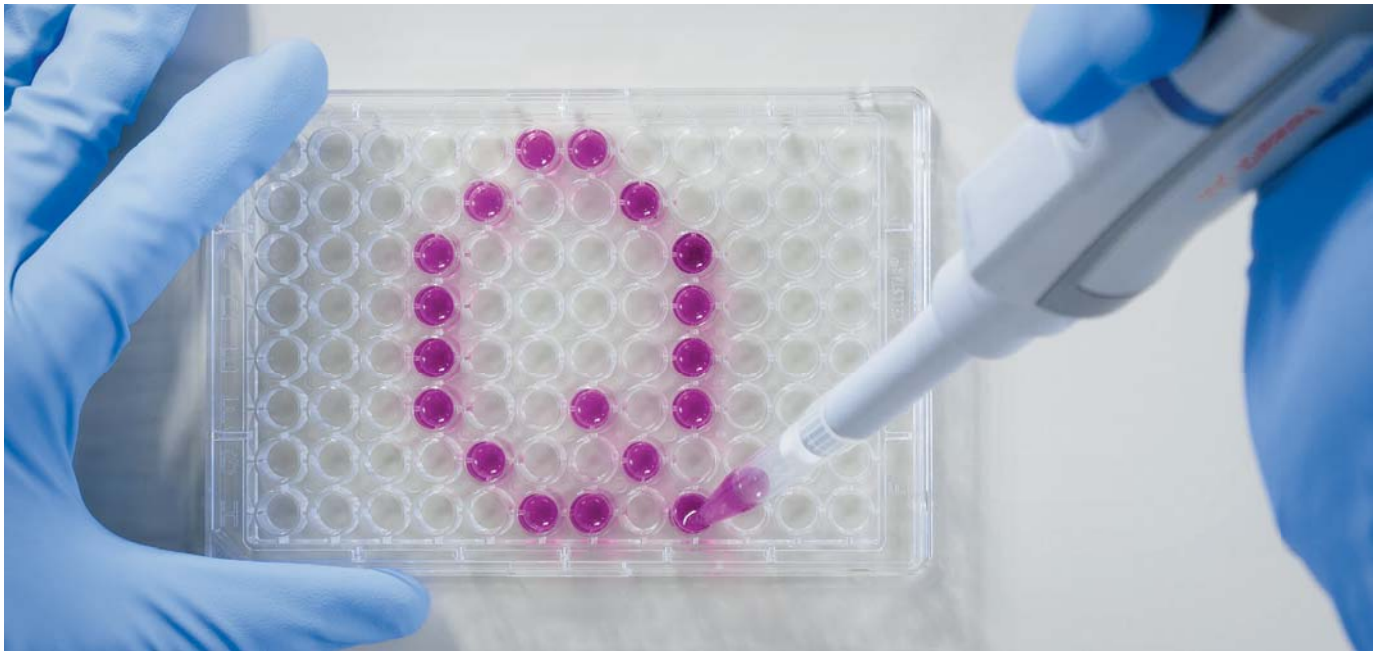

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# Getting Personal with Oncology

**Genomics offers much hope for cancer treatment, but we remain a long way from truly personalized medicine. Ex vivo screening will save lives, reduce unnecessary treatments and lead to the development of new drugs.**

*By Joe Olechno*

Many cancer drugs are effective in only a small percentage of patients. This raises a somewhat profound question: how do we know that a certain drug will work well for some patients? If a potential drug cures 3 percent of patients, the data may never be found in the population at large. Likewise, adverse effects on a different – but still small – percentage of the total population, may be lost.

One proposed solution is personalized medicine. Precision (or personalized) medicine has great potential, but most efforts focus on finding a genomic answer. Whether it is the National Institutes of Health website (1), or an interview with Joe Biden about the Cancer Moonshot (2), the technology focus du jour seems to be genomic analysis. Genomics has revealed much about cancer; it has led to new targets for therapy and offers much promise for the future, but it's important to look beyond the hype. The outcome of genomics-based testing is often less effective than proponents might imply.

I am far from Olympian, but I will beat you over a one-mile track if you hop the entire way… (3) And right now, we are hopping when it comes to personalized medicine if we rely completely on

genomics. To improve our outcomes, we need to use other tools alongside genomics. I believe there are three significant problems associated with the genomics approach to cancer treatment.

### Problem one: DNA mutations do not always cause cancer

Having a mutation, even a putative cancer-causing mutation, is not evidence of cancer, or of the cause of a particular cancer. Researchers at the Wellcome Trust Sanger Institute (WTSI) observed that healthy skin tissue is replete with somatic DNA mutations. In fact, those researchers found mutations in healthy skin at the same level as in tumor cells (4). Not only did a quarter of all healthy skin cells carry a cancer-causing mutation, but these mutations were under strong positive selection – that is, the number of cells carrying the mutations tended to increase.

In this case, if an oncologist found a "cancer-causing mutation" in a cancer patient, prescribing chemotherapy based on the finding would have no impact on the tumor. Unfortunately, the chemotherapy could still carry negative side effects for the patient, including mouth sores, hair loss, diarrhea, nausea, vomiting, and fatigue. Throughout this, the cancer, unaffected by the chosen course of therapy, would continue to grow and mutate.

Researchers at Johns Hopkins showed that DNA analysis of tumor cells tended to produce many false positives (5). They suggest that comparing mutations in healthy tissue with those in the tumor will determine the true, cancer-causing genes. Unfortunately, data from the WTSI shows that healthy tissue contains many different mutations. It is unlikely that there is a single healthy genotype to use for comparison.

*"Right now, we are hopping when it comes to personalized medicine if we rely completely on genomics."*

Problem two: Lab results vary

Quackenbush and colleagues compared genotypic and phenotypic results published by the Cancer Genome Project and the Cancer Cell Line Encyclopedia. They found that the two labs generated almost identical genomic results for 471 different cell lines (5). Yet, the phenotypic response of those cell lines diverged between the two labs. Where one lab found a particular drug to be effective in a cell line, the second lab gave contradictory results. Of the many drug/cell line combinations, only two of the 15 drugs tested in both labs showed any correlation. Chemotherapy based on the response of cell lines is problematic, at best.

Problem three: Personalized medicine is percentage driven

Most personalized medicine is not personalized at all – and is instead based on the responses of small patient groups. Therapy is based on how a percentage of patients with the same mutation and similar cancer responded. If the doctor determines the cancer-causing mutation among the somatic mutations, he or she may find a mutation for which there is no effective chemotherapy. The pharmacogenomic process can point you only to treatments that have already been verified in a population. While the

*"Most personalized medicine is not personalized at all – and is instead based on the responses of small patient groups."*

number of therapies grows, a genomics-based approach would miss cancers curable by drugs not associated with a particular mutation. If previous personalized medicine efforts have not linked a drug-mutation combination with a successful outcome, the doctor's options are limited.

### From hopping to running

How can we enhance the existing paradigm of personalized medicine to provide better cures? How do we move from hopping to running? The potential of genomics is great but we need orthogonal techniques as well. Researchers at the Institute for Molecular Medicine, Finland (FIMM) are developing an individualized approach to cancer treatment (6-13). At FIMM, they isolate cancerous cells from a patient and then test those cells against hundreds of possible drugs to see which are effective. They test drugs singly, and in combination, to identify those most potent against the patient's particular cancer cells. Even if a drug is only effective in one percent (or fewer) cases, it can still be discovered and prescribed.

Using this approach, FIMM researchers have identified treatments for patients who had already failed multiple rounds of traditional chemotherapy. They have also been able to save patients from ineffective treatments. In some instances, a drug may be effective against isolated cancer cells ex vivo, but may not work inside the body. But it is also true that if a drug does not work ex vivo, then it is unlikely to work in the patient. So, when DNA mutations suggest a particular drug, but ex vivo tests show that it will be ineffective in a particular patient, the FIMM protocol eliminates a futile round of chemotherapy. No loss for the insurance company, no chemo-induced side effects for the patient, and no wasted time during which malignancy can further develop.

FIMM's functional testing is not done in isolation. The researchers couple the results of the drug sensitivity tests with genomic results to gain information about the origin of the cancer and to help define new therapies to address new-found mutations. Using this technique, they showed that the anti-angiogenic renal cancer drug, axitinib, is very effective against a form of chronic myeloid leukemia (14). Such unanticipated repurposing of an existing drug is beneficial to both the patient and the drug manufacturer. These results suggest that other drugs that have passed Phase I – but failed to show efficacy in large-scale studies – could be repurposed.

Labs in Sweden and Spain are now expanding the efforts initiated by FIMM (15-18), but more labs must join the effort. Researchers in Spain have reported an ex vivo approach

*"Instrumentation, assays and cell manipulation techniques, however, are much more powerful today than they were 30 or 40 years ago."*

that keeps the tumor cells in their native microenvironment, significantly enhancing the quality of their results (19).

Chemotherapy has both monetary and health costs whether it leads to a cure or not. Every failed round of treatment reduces the window of opportunity to cure the disease. New methods, like those from FIMM, can save lives, reduce relapses, lessen costs, and help discover new drugs. So why don't we see researchers testing the FIMM protocols? And why don't we see extensive ex vivo testing occurring? When I mention the FIMM process to researchers, many have a few objections. Most importantly, they do not believe that they can get funding to do follow-up research since the technique failed to be effective in the 1970s and 1980s. Instrumentation, assays and cell manipulation techniques, however, are much more powerful today than they were 30 or 40 years ago. A greater impediment may be that researchers (and reviewers) think of personalized medicine as a genomics-based technique and do not consider the importance of orthogonal methods.

The combination of the ex vivo and genomics-based techniques brings a second leg to the race and running faster along this track is a boon to everyone: doctors, pharma companies, insurers, and – most importantly – patients.

*Joe Olechno is Senior Research Fellow, Labcyte Inc., San Jose CA, USA.*

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# Champion of Generics

**Sitting Down With... Abhijit Mukherjee,** Chief Operating Officer at Dr. Reddy's Laboratories, India.

How did your career begin?

When I graduated from Engineering School in India during the 1980s, I didn't have a specific career plan, but my family were keen for me to get working. At the time, the job market was dominated by a few large multinational companies – the main choices were either ICI or Unilever. I joined the latter as a management trainee in a very technical job (working with aroma chemicals and detergents), but it gave me the opportunity to work in different countries. Unilever did not encourage superficial learning, but rather the importance of going into the details. It was an important phase of my career – the early days are always a key learning experience. And working hard back then was always very much appreciated (not always the case today).

How did you transition to a business role?

I'd always had a liking for numbers – even on the shop floor I would attempt to connect any activity I was doing to a financial return. However, jumping from a technical role to a business role in the 1990s was not easy. Nevertheless, after around 13 years with Unilever, an opportunity presented itself at a large, technical conglomerate in India, where I was involved with the business end-to-end – from manufacturing, to sales, to dealing with banks and the collection of money. I ended up heading their biochemical and intermediates business, before Dr. Reddy's made me an offer in 2003 to join their management consulate.

What was Dr. Reddy's like when you joined?

At the time, Dr. Reddy's was an incubating business. Turnover was zero, but aspirations were high! I was interested in the challenge and destiny was kind. The company grew fast with some quick acquisitions, and we added an API business, which I ran for a while. I then moved into the core business, eventually becoming the chief operating officer around three years ago.

What are your main challenges in your current role?

The main challenges I face in my position are those which the whole generics industry faces. One major headwind is the huge number of mergers and acquisitions among pharmacy managers and retail chains in the US, which has boosted their bargaining power and created pricing pressures for generics manufacturers. The consolidation of channels has been a significant challenge for us, especially considering that over 50 percent of our business is in the US.

Another major challenge has been the increasing expectations from regulators – both in the US and elsewhere. Exports from India have rapidly increased in recent years and regulators have really stepped up to ensure high standards. I think the entire industry – ourselves included – has somewhat struggled to keep pace, but valuable lessons have been learned along the way.

Finally, macroeconomic turmoil in emerging markets has hit commodities hard. We have a fairly big presence in Russia, whose currency took a major hit in recent years, as well as Ukraine, where the situation has been even worse. But the good news is that those economies have stabilized more recently and, after such a dip, you tend to see a solid four or five years of growth. I'm optimistic about emerging markets, particularly as we've restructured and opened some new business avenues there. We've set ourselves in good stead to capitalize on the current period of stability.

What makes you the most proud about your work?

Dr. Reddy's spends in the region of 12 to 14 percent on research and development. What really makes me proud is when those passionate efforts generate societal benefits – especially in terms of access to medicines in underserved markets. One specific example we are currently working on is the creation of institutional businesses for oncology products in emerging markets. Access to oncology drugs is shockingly low in emerging markets – not because the prevalence of the disease is much lower than in the developing world, but because of issues around government funding. We are currently playing a significant role in delivering oncology medicines to patients in various countries across South America, Eastern Europe and Asia.

*"The main challenges I face in my position are those which the whole generics industry faces."*

If you could change one thing about the pharma industry, what would it be?

Changing the perception of the generics industry would be at the top of my wish list. I truly believe the generics industry is creating a great deal of value in terms of accessible and affordable medicines, both in developed countries and emerging markets. But negative attitudes are a constant barrier to generics, especially in emerging markets – it's an unspoken tragedy. There have also been a number of high-profile court cases around the world that have put the generics industry on the back foot. By changing perceptions, we might tip the balance of future, borderline cases in our favor – which I think would be of benefit to patients.

The generics industry seems to go through highs and lows, and I think it's currently going through something of a low, but I keep telling people that now is the time to be resilient and to have confidence in your values. If we do that, I believe the next decade will be a successful one.

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