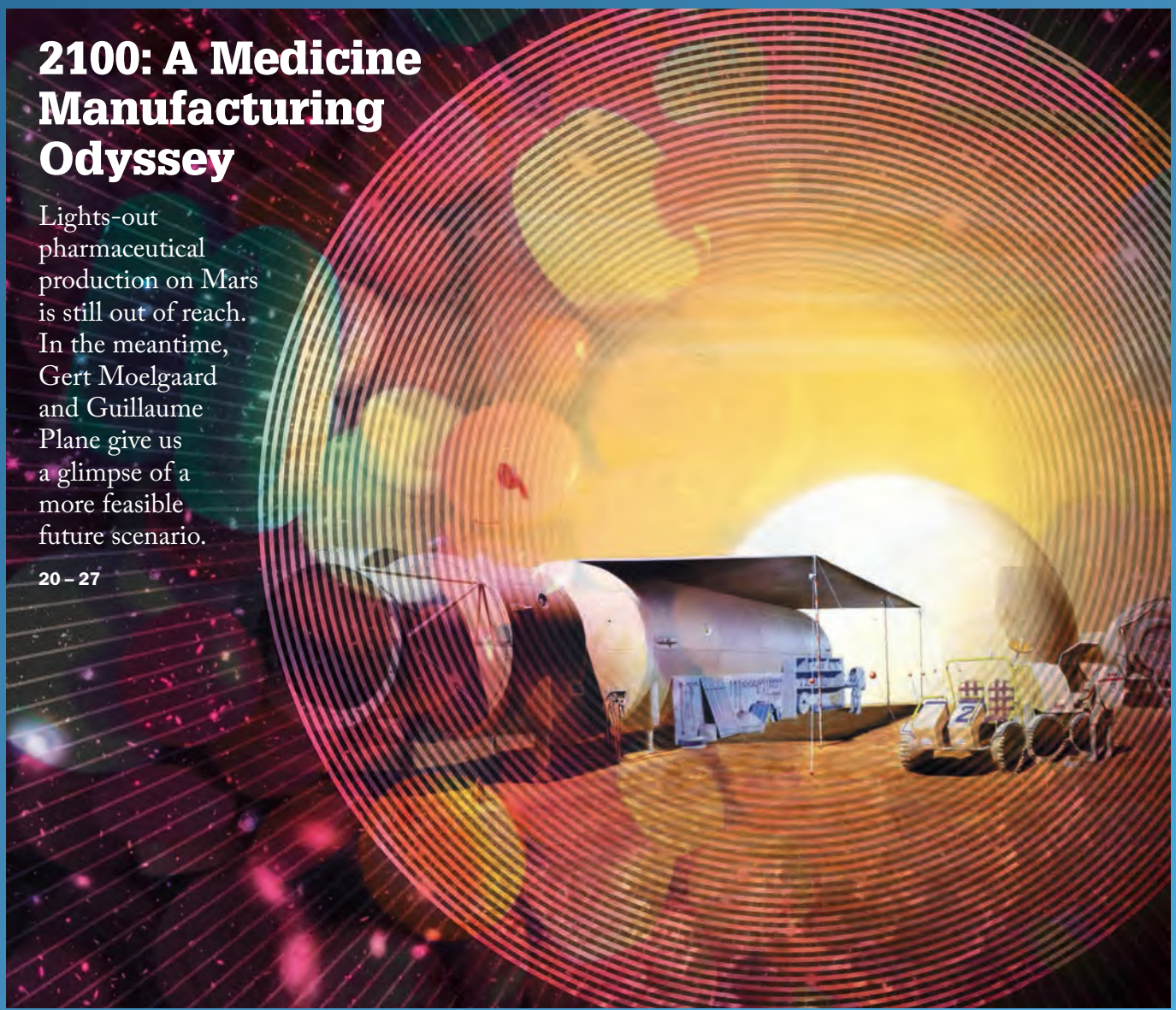
SEPTEMBER 2014 # 01

the Medicine Maker



2100: A Medicine Manufacturing Odyssey

Lights-out pharmaceutical production on Mars is still out of reach. In the meantime, Gert Moelgaard and Guillaume Plane give us a glimpse of a more feasible future scenario.

20 – 27

innovation loves a guiding hand

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

Vaishali Tawde,
an enabler in excipients

BASF
The Chemical Company

BASF excipients for solubilization.

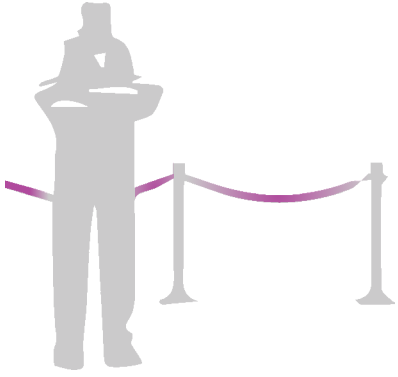
Contact us via e-mail at **pharma-ingredients@basf.com**
or visit **www.pharma-ingredients.basf.com**

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

Online this Month

Guest List

"If your name's not down, you're not coming in!"



The website really comes alive when you register. You can access all the printed content, plus find online exclusives and sign up for newsletters and alerts with further benefits over the next few months! themedicinemaker.com/login

Website

The Medicine Maker website acts as a hub for both our content and our community. Visitors can access all articles, engage with multimedia elements and interact through comments. Regular electronic newsletters and social media drive further activity on the website.

Social Media

Find more from The Medicine Maker. Connect and interact online through Facebook, LinkedIn, Google Plus, our YouTube channel and via Twitter (@medicine_maker)

Mile High Club

Content at 30,000 feet. The Medicine Maker iPad app is now available to download at the Apple App Store. Offering the ability to download and read content offline, it's easy to take The Medicine Maker wherever you go. To download the app and for updates on the upcoming Android version, visit: themedicinemaker.com/app

The Dotted Line .....

To guarantee your next copy of The Medicine Maker, sign up online and confirm your print subscription. And please feel free to pass this invitation onto colleagues. Subscription is qualified but free: themedicinemaker.com/login

Contents

20


50

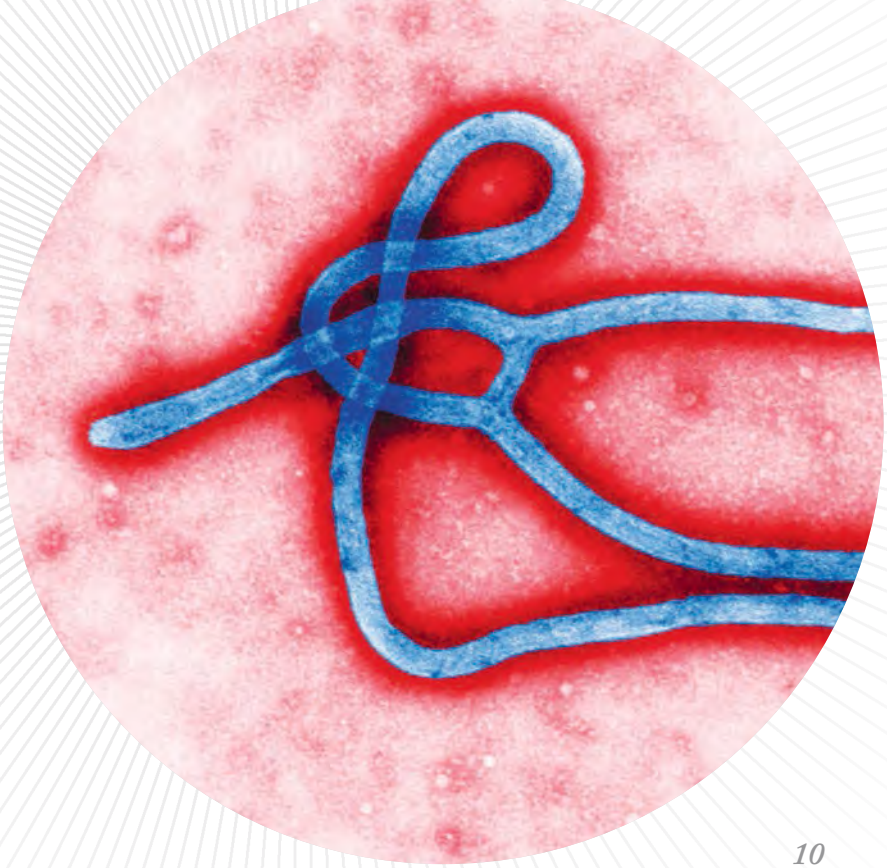

38

On The Cover

We take a flight of fancy to drug manufacturing on Mars. Background image courtesy of NASA/Mark Dowman.

Upfront

In My View



10

Feature

Best Practice

NextGen

Profession

Sitting Down With

the Medicine Maker

ISSUE 01 - SEPTEMBER 2014

Editor - Charlotte Barker
charlotte.barker@texerepublishing.com

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

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

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

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

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

Publisher - Richard Hodson
richard.hodson@texerepublishing.com

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

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

Traffic and Administration Manager - Claire Lally
claire.lally@texerepublishing.com

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

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

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

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

Distribution:
The Medicine Maker is distributed worldwide through 17,000 printed copies to a targeted European and North American mailing list of industry professionals and 60,150 electronic copies worldwide.
ISSN 2055-8201

texere publishing ltd

MAb polishing on your mind. Our Capto™ S ImpAct.

We developed Capto S ImpAct for efficient MAb aggregate removal to improve your productivity and cost-efficiency. With an extended-surface ligand, Capto S ImpAct offers high binding capacity and excellent resolution, even at high sample loads. When MAb polishing is on your mind, we are a partner like no other.

upstream downstream single-use services

Learn more at: **gelifesciences.com/CaptoSImpAct**

GE works.

www.gelifesciences.com/CaptoSImpAct

Welcome to the first issue of The Medicine Maker. The creation and delivery of therapeutics draws on the talent, passion and expertise of a wide range of professionals. We want to bring this group into the spotlight. From Phase I clinical trials to market launch and beyond, we want to bring together the many threads that make up drug development and manufacturing. There is no more interesting, challenging or important area to be working in, and that will be reflected in every issue of the magazine.

Our aim is to bring you useful, credible and entertaining articles, in print and online. Specifically, we have three guiding principles for developing our content.

The first is to tell stories. We go below the surface to delve into the hopes, fears, motivations and aspirations of the key figures. We believe that these personal stories provide a deeper appreciation of the field, and a fuller understanding of where it is headed.

The second is to generate practical, pragmatic articles that are meaningful to your daily working life. We bring the world's leading experts to you so that they can share experiences, opinions, insight and advice that you won't find elsewhere. This will include articles that review best practice, and evaluate new technologies and initiatives that will shape the industry. Furthermore, we will extensively cover topics that will improve your on-the-job performance, including personal and career development, advice on managing projects and staff, and analyses of the interface between the many specialties that work together to develop new drugs and biologics.

The third is engagement. The content that we publish is a starting point, not an end point. We want your feedback, suggestions, and submissions on every aspect of the development and manufacture of new pharmaceuticals. Our goal is to create a publication that you look forward to receiving every month – a new type of publication, full of content that will be useful, entertaining and inspiring.

You can engage with our content in whatever format you prefer – in print, PDF, iPad app or online at www.themedicinemaker.com.

We will judge our success on how well we meet your needs, so please let us know what you like, what you don't, and what you want to see us cover. It's your publication.

Charlotte Barker
Editor

Bob Dvorak and Rick Johnston

Before Bob Dvorak developed his current passion for data management and went on a curious journey that led from research labs, to biotech start-ups, to major software vendors, to a small consulting practice, he earned his PhD from the Ohio State University. He is currently focused on helping provide strategic guidance around electronic systems and data management as one of the principals of BioPharma Data & Manufacturing Systems Consulting. "Because I really don't understand the concept of just doing one thing at a time, I am also continuing to work on an eight-book series of novels that I've been writing for the past 30 years… I might finish sometime in the next 30."

Rick Johnston hails from New Zealand and is a pioneer in risk assessment, planning and operations in biopharmaceutical manufacturing. He currently works with more than 30 percent of the world's biomanufacturing capacity, managing their supply chains and production processes. He is the CEO of Bioproduction Group, where he builds software tools, and is also a professor at Keck Graduate Institute, part of the Claremont Colleges in California. He is obsessed with Lego and enjoys building sets with more than 3000 pieces.

Get Bob and Rick's tips for optimizing your digital biomanufacturing enterprise on page 30.

James Agalloco

Jim Agalloco is an industry veteran of some 40+ years; 20 years in big pharma (Merck, Pfizer, Squibb, and BMS) and another 20 years as a consultant to firms large and small. "I've had the good fortune to work in many different areas – API, biotech, sterile and non-sterile products." A life-long learner, Jim says: "I solve puzzles for a living. It's a fun challenge because the picture is not on the box. There may be pieces missing and it often has to be done against the clock. My publications, training offerings and participation in the Parenteral Drug Association and United States Pharmacopeia allow me to give back a lot of what I've learned."

Read about Jim's view on hold times for sterilized items on page 17.

Markus Hartmann

"Following the evolution of research and development from a bird's eye perspective is a highly interesting and awarding endeavor," says Markus Hartmann. "After completing my PhD in medicinal chemistry investigating new anti-tumor agents in 1996, I was interested to learn how the molecules are then tested in humans and, later on, how all the data compiled on a new agent are compiled for marketing authorization purposes." Having taken over roles as medical advisor in pharmaceutical corporations or as regulatory consultant serving scientific networks, Markus admits that combining scientific rigor, medical and clinical expertise, and regulatory and legal knowledge under one hat is a great challenge, but a continuously stimulating experience for his present and future work. His specific interest lies in the regulatory and legal questions that surround clinical research for drugs, devices and diagnostics.

Markus deciphers the EU's new clinical trials regulation on page 16.

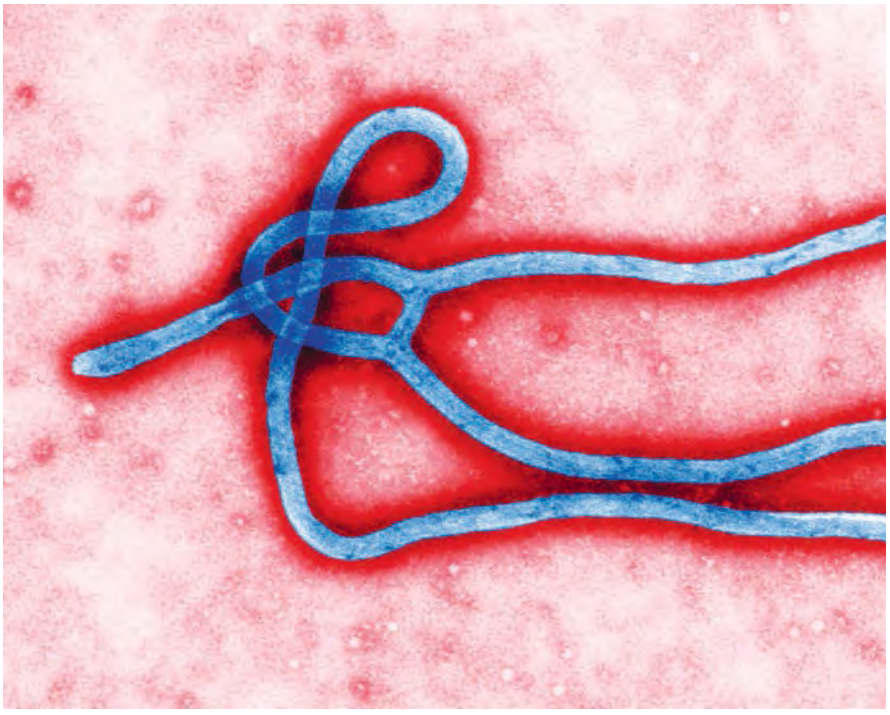

WORLDWIDE. Raised blood pressure is estimated to cause 7.5 million deaths annually – about 12.8% of the total of all deaths. Raised blood pressure is a major risk factor for coronary heart disease and stroke.
CHINA. AstraZeneca is building a new facility for production of oral solid dosage products, including Betaloc, which is used to treat high blood pressure.
nne pharmaplan®
Engineering for a healthier world

Upfront

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

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

Email: charlotte.barker@texerepublishing.com



World War Ebola

New vaccines, experimental treatments for patients, and cash donations make their mark on the Ebola outbreak.

In one of the latest updates to the unfolding story of Ebola, a vaccine developed by GlaxoSmithKline (GSK) and the US National Institute of Allergy and Infectious Diseases has entered Phase I human clinical trials after being fast-tracked by the FDA. GSK added that it will also be manufacturing around 10,000 extra doses of the vaccine that will be immediately available to high-risk communities, if the trials are successful. GSK hopes that the trial will be complete by the end of this year.

According to the World Health Organization, the current Ebola virus disease epidemic in West Africa, considered the largest since the virus was first identified in 1976, has seen more than 3,600 cases, with the fatality rate averaging around 50 percent (1). Towards the end of August, a separate, unrelated outbreak was also confirmed in the Democratic Republic of Congo.

GSK's vaccine is against the Zaire species of Ebola (the strain currently affecting West Africa) and is based on an attenuated strain of chimpanzee cold virus, chimp adenovirus type 3; the adenovirus is used as a carrier to deliver genetic material derived from the Ebola virus, and has apparently shown positive results in monkeys.

GSK is not the only Big Pharma company jumping into action. In early September, Johnson & Johnson (J&J) announced that it had teamed up with biotech company Bavarian Nordic to fast-track a combination vaccine against Ebola that uses a prime–boost regimen. The vaccine is based on AdVac technology (developed by Crucell, which J&J acquired in 2011) and Bavarian Nordic's MVA-Bn technology. Clinical trials are expected to begin in 2015, and J&J is

also reviewing known pathways in Ebola pathophysiology to see whether previously tested medicines could be useful as treatments.

Mapp BioPharmaceutical has also been working on a potential Ebola treatment: ZMapp, which has been discussed extensively in the media. ZMapp is a combination of three monoclonal antibodies (mAbs) manufactured in tobacco plants, and was first announced as a drug candidate in January 2014. The mAbs bind certain virus proteins and help to neutralize the virus. Although it's only been tested in animals so far, it has been given to a number of Ebola-infected patients. Some of these patients have recovered, although it is not known if their survival can be attributed to Zmapp. The company was recently awarded a federal contract to help accelerate testing and increase production yields.

Other companies have also come forward to offer their own experimental Ebola treatments, including Fujifilm and Sarepta Therepeutics. TKM-Ebola, an RNAi therapeutic developed by Tekmira, is another experimental treatment in the works. The drug went into Phase I clinical testing earlier this year, but was put on partial clinical hold by the FDA because of safety concerns. Tekmira says it is evaluating options.

Outside of the pharma industry, governments and other organizations have also come forward with cash donations to help contain the outbreak. One of the most recent – and largest – donations was $50 million from The Bill & Melinda Gates Foundation.

New developments and donations are coming to light almost every day. We'll keep you updated on the outbreak on our website with exclusive Q&As and more. www.themedicinemaker.com. *SS*

Reference

1. *WHO, Ebola virus disease outbreak - West Africa, September 2014, www.who.int*

FDA's Most Wanted

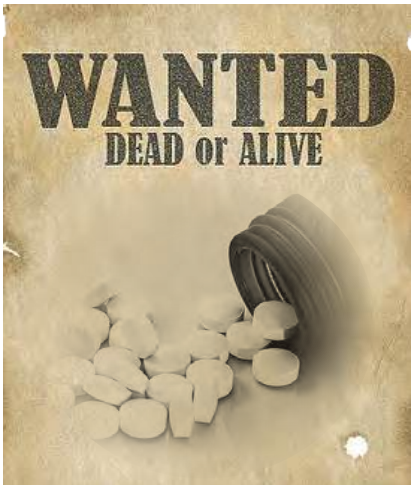
Top food and pharma fugitives are named and shamed.

You've most likely heard of the US FBI's Most Wanted. In fact, most countries have their own list of criminals to raise public awareness. Now, the FDA has decided to take a similar approach to track down several elusive fugitives connected to criminal acts involving food and regulated medicines (1).

Eleven names made the list and, as you might expect, many of the suspects are involved with counterfeit pharmaceutical products. Other offences included drug diversion, writing false prescriptions, selling fake stem cell injections direct to patients and, in the only case related to food, passing off catfish as "other" fish. You can read the full list and the dark stories behind them on the FDA website.

The FDA is keen for as many people as possible – worldwide – to take a good look at the list. "The fact that many of the Most Wanted are not US citizens highlights the truly global scope of our job, which is to protect the integrity of all the products the FDA regulates," says an FDA spokesperson. "Further, foreign-based suspects are particularly difficult to locate and take into custody. Our Office of Criminal Investigations (OCI) continues to work with our international partners, especially Interpol and Europol, to help bring these fugitives to justice."

The high value of pharmaceutical products is a strong lure to criminals and the FDA is regularly involved in criminal investigations. In August alone, the FDA published nine press releases about different criminal cases connected to medicines, with the offenses ranging from smuggling adulterated cancer drugs, distributing unapproved foreign drugs, and healthcare fraud, to a man



selling prescription drugs made in his own home with ingredients purchased from China.

In a July 2014 report, Interpol explained that several of its member countries have reported increases in pharmaceutical crime in the past five years, particularly in South and Central America (2). In one South American country, illicit profits were found to be almost one-third of the profits made in the legal pharmaceutical market between 2008 and 2012.

A key trend in many countries has been the increased use of illicit online pharmacies, operated by both informal networks and organized criminal groups. Increasingly, law-enforcement agencies are also dealing with criminal organizations that use sophisticated international networks, which are difficult to target. Interpol added that corruption within the ostensibly legal pharmaceutical industry and a lack of enforcement units (as well as legislative challenges in some countries) is making it difficult to tackle the problem. *SS*

References

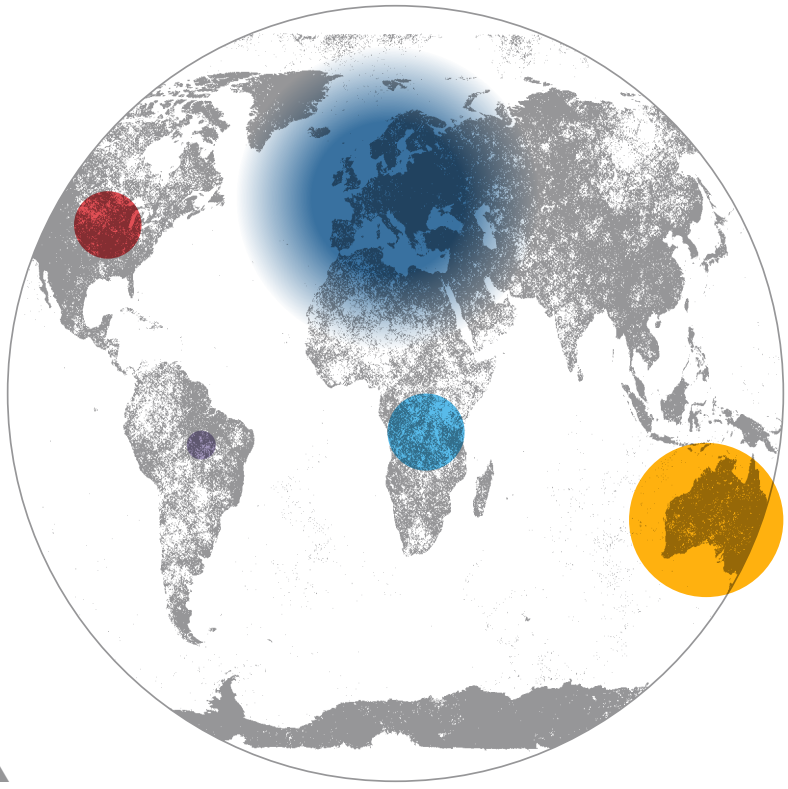
1. *Office of Criminal Investigations (OCI) Most Wanted Fugitives, www.fda.gov*
2. *Interpol, Pharmaceutical Crime and Organized Criminal Groups, July, 2014*

CPhI in Numbers

In October, CPhI Worldwide 2014, along with ICSE, P-MEC and InnoPack, comes to the City of Light - Paris. Here, we bring you some key facts and figures about the event.

CPhI focuses on ingredients, including APIs, excipients, custom manufacturing and finished formulation, while co-located events ICSE, P-MEC and Innopack cover contract services, equipment and packaging. Bringing together pharmaceutical companies and suppliers, the exhibition covers 60,000 m² (so comfortable shoes are a must).

Amidst all that networking, don't miss the Pre-Connect Congress on October 6th, with talks from Alan Sheppard (IMS Health), Trevor Jones (Allergan, USA) and Sudhanshu Pandey from the Indian Ministry of Commerce and Industry.

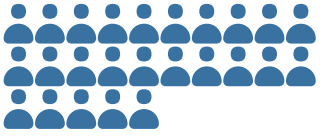


▲ *Visitors by region (2013)*

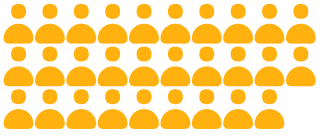
- *Europe (Western & Eastern) 66%*
- *Australasia (Asia, SEA, Australia, Pacific) 16%*
- *Africa & MENA 8%*
- *North America 7%*
- *Central and South America 3%*

Attendance numbers

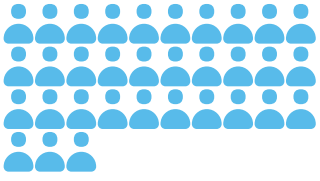
2009, 25,147



2011, 29,920 ▲ *4,773*



2013, 33,969 ▲ *4,049*

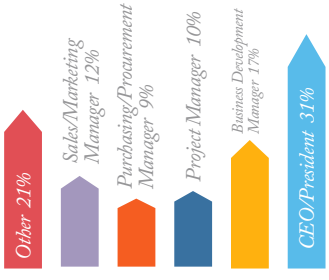


Exhibition times

Tuesday 7 October 2014	*09:30 am - 17:30 pm*
Wednesday 8 October 2014	*09:30 am - 17:30 pm*
Thursday 9 October 2014	*09:30 am - 16:00 pm*

Number of exhibitors

Visitor job position (2013)



Total floor area of show's coverage in m²

2009, 46,546
2011, 53,103 ▲ *6,557*
2013, 57,924 ▲ *4,821*

Controversial Shuffle for EC Pharma Policy

European Commission (EC) plans to transfer governance of the medicines dossier from health to enterprise has upset public health NGOs.

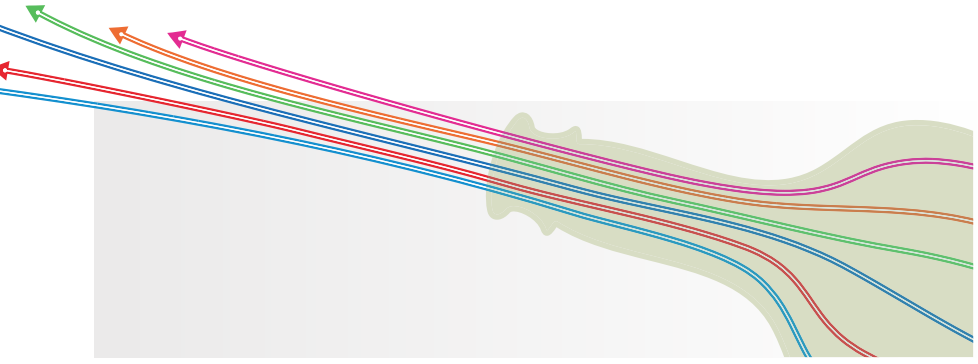
As part of incoming President Jean-Claude Juncker's reshuffle of the EC Commission, responsibility for health technology and pharmaceutical policy is being shifted from the Health and Food Safety Commissioner to the Commissioner for Internal Market, Industry, Entrepreneurship and SMEs.

The decision has been greeted with alarm by public health organizations; among others, the European Public Health Alliance (EPHA) and European Consumer Organization have released statements condemning the move, claiming that the change will impede the Health Commissioner's ability to manage a coordinated response to a public health crisis, such as a major disease outbreak. They are also concerned about the potential to skew drug policy towards the interests of pharmaceutical companies.

In protest, the EPHA – whose members include nearly 100 public health NGOs across Europe – has withdrawn its support for the proposed Health for Citizen's Intergroup in the European Parliament. In a statement, the Alliance said "This change makes our support for the proposed Intergroup untenable and in direct contradiction with our core position that health and healthcare should be led by public health interests and the public good." *CB*

Reference

1. *EPHA Press Release, "Juncker puts Europe's security at risk by promoting profit over public health" (September, 2014).*



Translation Twists and Turns

Could tackling bottlenecks in early-stage R&D provide a faster route to the clinic?

Efforts to speed up clinical translation of new therapies typically focus on moving the product from R&D into clinical trials – that is, from bench-to-bedside. A new study has revealed just how often new drugs move around between different companies during this process. The classic pathway for therapies discovered in a university lab is for the IP to be licensed to a small biotech company, with a view to sublicensing to a larger company for clinical trials. However, it is not uncommon for drugs to move around several companies during early-stage development. Could streamlining these bench-to-bench moves be another route to accelerate commercialization?

Researchers from the Georgia Institute of Technology wanted to find out just how pervasive the churn of early-stage molecules is (1). They looked at 342 university licenses with biotech firms, covering 835 patents, and followed the patents through the initial licensing from university to industry, and subsequent sublicensing. They found that around 27 percent of the patents studied had been granted a second license, with only a small proportion actually in clinical trials or beyond. A high proportion of drugs also showed changes in indication between first and second license. As the authors point out, early-stage drug development is "anything but linear", which results in frequent re-setting of the R&D clock, as basic research is repeated for different indications and by different companies.

The authors suggest that better communication of the results of early research could speed up the process by cutting down on repetition, and recommend a translational research database similar to clinicaltrials.gov. Study author Marie Thursby explains, "This should allow firms to more easily find partners, for policy makers to more accurately deploy research funding and, hopefully, prevent actors from duplicating or triplicating research efforts. Better information, for example, would allow many disease foundations to more easily identify research relevant to them, which they could in turn support." *CB*

Reference

1. *M. J. Higgins, J. Thursby, and M. Thursby, "Bench-to-Bench Bottlenecks in Translation", Sci. Transl Med. 6 (250), 250fs32 (2014).*

Copycat Drug Drama

Lilly and Sanofi go head-to-head on a diabetes drug. Meanwhile, Hospira sues the FDA over a new generic approval.

Eli Lilly and Boehringer Ingleheim recently announced that the FDA has granted "tentative" approval of their insulin glargine injection, which they plan to market as Basaglar in the US (1).

But the drug won't be available to patients for some time. Sanofi has filed a lawsuit claiming patent infringement of their insulin glargine drug, Lantus. Under the Drug Price Competition and Patent Term Restoration Act, this means an automatic stay of up to 30 months while the case comes to court.

The drug was filed through the FDA's 505(b)(2) regulatory pathway, which considers the safety and efficacy of existing drugs alongside data from clinical trials of the new drug. In Europe, the drug is considered a biosimilar and has been recommended for EMA approval by the advisory Committee for Medicinal Products for Human Use (CHMP).

Hospira is also unhappy. A temporary restraining order blocking the sale of generic versions of its patented sedative, Precedex, has been lifted (2). It was only last month that Hospira brought the lawsuit against the FDA and two companies planning to sell the drug (Mylan and Par Sterile). It was a US district court judge that issued the restraining order, but now the court has issued a summary judgment in favor of the FDA and generic drug makers.

Hospira called the FDA's approval of the copycat drugs "arbitrary and capricious" and warned that the decision is likely to lead to substantial job losses – most of the Precedex sales team will probably be axed. The company is taking its case to the court of appeals, and has asked for another restraining order to be granted until it can be heard. *CB*

References

1. *Boehringer Ingelheim Press Release, "FDA Grants Tentative Approval for Lilly and Boehringer Ingelheim's Basaglar™ (insulin glargine injection)" (August 18, 2014).*
2. *RTT News, "Mylan, FDA Granted Favorable Summary Judgment By Court On Generic Precedex" (September 8, 2014).*

You Direct.

Mobius® CellReady Bioreactors Perform.

Picture this: You now have single-use, stirred tank bioreactors that deliver the ultimate in flexibility, reliability, and ease of use for mammalian cell culture.

Imagine:

- Simple, reliable installation
- Configurable process monitoring at point-of-use
- Automation platform of your choice

All backed by a world-class supporting cast of technical experts and application engineers to optimize your cell culture results.

Simple, smart and reliable.

Picture a great performance, every time.
Picture Mobius® CellReady Bioreactors
www.emdmillipore.com/mobius

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

In My View

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

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

Contact the editors at edit@texerepublishing.com

Clinical Compromise for Europe

After years of intense criticism, the European Parliament has adopted a new regulation for clinical trials that will replace the current EU Clinical Trials Directive by mid-2016. But is it enough to reverse a decade of decline in European clinical research?

By Markus Hartmann, Principal Consultant, European Consulting & Contracting in Oncology, Trier, Germany.

How can I succinctly share an ambivalent attitude on a major overhaul in Europe's clinical drug regulation? How can I quickly summarize 76 pages of legislation (1), with 85 recitals, 99 articles, 24 definitions and seven annexes. First, I will assess where the new regulation has succeeded. Then, I will turn a critical eye on what has been missed.

The European Commission (EC) took the right path in autumn 2007 when it organized a stakeholder conference to discuss the multiple signals of dysfunction that had emerged since the first-ever pan-European legislation on clinical drug research came into force in May 2004.

After two consecutive stakeholder consultations, the EC published an impressive proposal for regulation of clinical trials in July 2012. With a splendid blend of decision analytics and imagination, the EC managed to conserve the positive, internationally competitive elements of the legislation already in place (notably the rather short authorization timelines), in addition to overcoming many of the limitations of the current European framework. Here are five key points:

1. A web-based 'EU-Portal' will facilitate communication between trial sponsors, national authorities and ethics committees, considerably reducing the administrative burden.
2. Dossier requirements are set directly by the regulation, giving the promise of real harmonization. A single 'reference member state' will be in charge of the assessment of the investigational medicinal product dossier and will act as a contact point throughout the process, from initial dossier review until publication of the final study report.
3. National requirements (informed consent, patient information, data protection, liability and damage compensation) will be bundled in the so-called 'Part II' of the submission dossier. Member states can 'opt-out' of participating in the trial, if concerns are raised by ethics committees or other national authorities.
4. There will be one fee to pay per participating country: this competitive element will contribute to further reduce red-tape and strengthen the position of those EU countries, such as the UK, that have streamlined their authorization and supervision processes.
5. The principle of risk proportionality will facilitate more risk-adequate trial authorization and supervision processes. A category for 'low-intervention clinical trials' has been established to allow a less burdensome assessment of standard treatments and therapy optimization of marketed

medicines by clinicians. Plus, article 48 explicitly allows sponsors to "determine the extent and nature of the monitoring," taking into account the characteristics and risk features of the trial.

Unfortunately, not all of the proposed measures survived the institutional decision-making process (known as 'the trialogue' in political slang). Among the victims were the proposal to tackle insurance costs by "national indemnification mechanisms" in each member state; the concept of streamlined authorization processes through 'appropriate bodies' similar to the Dutch Central Commission for Medical Investigations (an empowered national ethics committee); the very competitive timelines for trial authorizations; and practical simplifications, such as a reduced archiving period (from 15 years to five) for trial master files at sponsor and investigators' sites; parliamentarians actually voted to prolong the archiving time of the master file to 25 years, in the false belief that such a move will enhance patient safety.

Our industry must also accommodate a new passenger that came on board during the institutional process: transparency. Clinical trial transparency has been in the media spotlight and the subject of much debate, and is now enshrined in the new regulation; full study reports will now be available to the public. This move will not only affect trial reporting, but also the way industry investigates clinical pharmacology and biomarker features in future pivotal trials in the EU, as this valuable knowledge, once made public, might be used at a rather early stage by competing companies for their own purposes too.

The new rules will certainly help facilitate pan-European trials and offer relevant treatment opportunities for patients with rare diseases. But will they reverse the observed decline in Europe's clinical drug research? In my view, the resulting legislation is a typical European compromise that could have sent a much stronger signal for simplification and innovation. I, for one, will be eagerly awaiting outcomes research that tracks the number of trials authorized after the legislation comes into force in 2016.

Reference

1. *Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Official Journal of the European Union, L158 (2014). http://eur-lex.europa.eu*

Aseptic 'Warehouse' Danger

Is there a 'safe' hold time for sterilized items? And, if so, how can those hold times be reliably validated?

By James Agalloco, Agalloco & Associates, New Jersey, USA.

Many items need to be sterilized for aseptic processing, including stoppers, filler change parts, utensils and more, so for ease of operation it is common to maintain an inventory of ready-to-use parts in the aseptic core. Unfortunately, I've seen this taken to the extreme, with many sites essentially becoming a 'warehouse' of pre-sterilized items, with hold times as long as a month…

Long hold times have their advantages in terms of operational flexibility, but I'd argue against them from an aseptic processing perspective. In fact, I'd say that an aseptic warehouse of any size is just about the worst idea ever. The packaging for the sterilized items may be integral, but the additional handling required to keep them in the aseptic core for an extended period is always risky. Unfortunately, the practice of establishing a warehouse is all too common. It simplifies the planning process and allows for easy schedule changes because all of the required items are already available. What is sacrificed for all this convenience is the ability to maintain environmental conditions and item sterility. Don't forget that all rooms, surfaces and items should be sanitized on a frequent basis, which includes storage areas and stored items.

The best approach to material supply in aseptic and clean filling is to adopt a 'just-in-time' approach by maintaining minimal inventory in the aseptic core. When items must be stored, it's important to minimize the risks. The key here is to have an effective wrapping system. I prefer press-sealed bags, which are widely available and have a porous side for air/condensate/steam exchange. A much less capable wrapping technique that I've frequently seen is covering items in paper or cloth sheets that are then tied or taped to offer some measure of post-sterilization protection. Such wrapping is perfectly acceptable for birthday presents, but it's too variable for aseptic items that are to be held sterile for any length of time. The integrity of the final package is nothing like that of press-sealed bags. They may be inexpensive but that does

not justify their use.

When it comes to validating hold times, the only method I believe appropriate is associated with aseptic fills: you hold the items in the aseptic core and then use them in a process simulation (media fill test). If the media fill test works then you've confirmed the acceptability of the hold time. You can schedule the media fill a day or two longer than the actual hold time you intend to use routinely, bearing in mind that the hold period should always be minimized as much as possible.

Establishing hold times via sterility testing of wrapped items is a much less appealing approach. The manipulations involved in sampling and testing these materials are very different from the methods used for testing the product itself and have the potential for false-positive results.

I would set the hold time requirement for all products, both aseptic and terminally sterilized, using the results from the validation tests. However, it's important to understand that the media fill test does not include every permutation of component or equipment – another argument against the gift-wrapping approach to sterilization component protection, where every item will be wrapped differently. Applying consistent wrapping methods to all items enables the firm to use the same validation data across the board.

Medicines and the Microbiome

We now know more than ever before about the complex ecosystem of bacteria, fungi, and viruses within our bodies. How can that knowledge be best applied in drug development and manufacturing?

By Tim Sandle, Head of Microbiology, Bio Products Laboratory, Watford, UK.

The human body plays host to trillions of microbial cells across the epithelial surfaces of the mouth and gut. These communities of microorganisms – collectively, the human microbiome – have crucial roles in human physiology and organ function, particularly in digestion and immunity. They may also have significant impacts, both positive and negative, on the effectiveness of medicines.

Fortunately, we now have a greater scientific understanding and appreciation for the microbiome than ever before – mostly thanks to the efforts of the Human Microbiome Project (HMP), a US National Institute of Health initiative launched in 2008. HMP's goal is to identify and characterize the microorganisms associated with both health and disease, and many of the findings have implications for the way that medicines are formulated and the environment in which they are prepared. The truly exciting aspect of this work is that it reveals, for the first time, the extent to which the human body is host to a vast array of different microbes. But this isn't just an area of academic intrigue; interactions between the human body and its microorganisms are vital for human health.

Understanding the intricacies of co-metabolic activity that occur amongst individual bacterial populations, pharmacologically derived byproducts, and the human gut has become a subject of much research. The microbiome regulates metabolic balance and homeostatic activity, adapting to each individual and their environmental circumstances, which makes all medicines unintentionally 'personalized' in a way. Indeed, the extent to which the microbiome influences the relative effectiveness of drugs in different individuals is a fascinating topic with great potential. It is not hard to imagine a new era of personalized medicine, when an individual's microbiome might be screened to ensure that a particular medicine targets only certain parts of the body, perhaps working in conjunction with some microorganisms whilst avoiding degradation by others.

But that's the future. One area that has seen immediate increased attention as a result of HMP's work is contamination. We all know that non-sterile medicines, such as creams and ointments, must be protected from specific pathogens, while any contamination at all of sterile products can be extremely dangerous. However, the HMP has shown that the microbiome of the human skin is more diverse than previously thought, demanding a rethink of several aspects of sterile production, from improvements in the types of cleanroom clothing worn to the way that clean filtered air is provided and circulated. We each shed a billion skin cells per day – that's 30,000 to 40,000 dead skin cells every minute – and approximately 10 percent of those cells play host to microorganisms. Clearly, those tasked with designing controlled environments must guarantee clean air spaces that effectively remove any contamination dispersed by operators (through turbulent air-flow), verify that disinfectants have appropriate biocidal activity, and ensure that staff changing procedures are sufficiently robust.

Now that the HMP has provided us with new information about the richness and complexity of the bacteria, fungi, viruses and other organisms that live

in intimate contact with us, it's crucial that we apply this knowledge across the board. Deeper knowledge of the human microbiome can help us develop new, optimized or even personalized medicines, but it can also ensure that medicines are not contaminated with microbial populations that might interfere with their action or otherwise cause harm.

Facing up to Neglected Diseases

The World Health Organization has compiled a list of 17 tropical diseases that deserve higher priority. Is the pharmaceutical industry solely to blame for a lack of progress?

By Faiz Kermani, President of the Global Health Education Foundation, CT, USA, www.globalhef.org.

The incredible medical advances of the past few decades promise an even more exciting future to tackle disease – for some. Shocking healthcare disparities continue to exist on a global level and many people lack access to even basic healthcare. In underserved populations, diseases have a severe impact on health outcomes and this is compounded by poor infrastructure, lack of resources, inefficient delivery of services, and corruption. Unfortunately, we are witnessing all these factors at play in the response to the current Ebola outbreak in Africa.

The World Health Organization (WHO) has estimated that more than one billion people suffer from one or more neglected diseases (1); another sad truth is that neglected diseases further worsen poverty over the long-term since they often affect children, restricting their school attendance and educational outcomes.

As neglected diseases do not promise a high return on investment, most companies have been reluctant to work in this area. It is this general lack of commercial interest from the private sector that has led to the exploration of other models, such as public–private partnerships (PPPs). As the name suggests, PPPs draw on the expertise of the public, private and academic sectors, with each party contributing according to their own area of strength; importantly, the costs and risks are shared. And though PPPs have made a difference in stimulating research for neglected diseases, getting products to market and into effective use remains a challenge.

Many believe that regulatory authorities should play a more prominent role, perhaps creating more attractive regulatory mechanisms to encourage drug development for neglected diseases or offering companies special incentives. But in practice, it has been hard for regulators to put forward ideas that find universal acceptance; for example, the FDA can now award a priority review voucher (PRV) to a company that obtains approval for a product that prevents or treats a neglected disease. PRVs can then be used to accelerate regulatory approval of another drug in any disease indication. Eliminating months from the standard FDA review allows earlier market entry, but some aspects of the PRV mechanism, such as the fact that vouchers are transferable and can even be sold to another company (2), have led to concerns over the commercial intentions of companies seeking them. In any case, the existence of this regulatory mechanism has not led to a surge of drug development activity for neglected diseases.

And though there is a clear need for the pharmaceutical industry to develop new drugs for neglected diseases, this alone will not help solve the basic healthcare problems facing communities in developing regions. In many cases, straightforward and effective strategies are actually available to control and eventually eliminate many of the health conditions affecting underprivileged populations, but access even to those medicines is a huge problem, as discussed in an interview with Access to Medicine Foundation CEO Wim Leereveld on page 50.

Any progress in developing drugs for neglected diseases will only translate into better healthcare for communities if operational and infrastructure issues are also addressed. Furthermore, all efforts must be aligned with improvements in complementary development areas, such as poverty reduction, nutrition, water and sanitation, women's empowerment, and education.

Initiatives to reduce healthcare disparities in developing regions require long-term financing, provision of healthcare resources, educational programs for communities and health workers, collaboration between different stakeholders and political commitment. The pharmaceutical industry has an important role to play, but it alone cannot provide all the answers.

References

1. *The 17 neglected tropical diseases, World Health Organization (2014), www.who.int*
2. *FDA priority review voucher for neglected diseases to be auctioned, Global Health Technologies Coalition (2014), www.ghtcoalition.org*

The Future of Medicine Manufacture

Economic pressures, new technology and the rise of biologics are all having a huge impact on the pharmaceutical industry. What will the next 10 years hold for drug and biologics manufacture? To answer that question, Gert Moelgaard reviews the factors driving big change in manufacturing and Guillaume Plane takes us on a tour of the facility of the near future.

The New Pharma Reality

As pharmaceutical companies adjust to life after the patent cliff, how are changing trends and fresh challenges affecting the world of medicine manufacture?

By Gert Moelgaard

For almost a decade, the theme I've heard talked about over and over in the pharmaceutical industry is the patent cliff and its anticipated impact on business and profits. Today, most companies are past this precipice, but the world on the other side is very different to the one we were used to. I call this the "new pharma reality."

Many articles over the last five years have described the consequences of the patent cliff. They predicted that between 2010 and 2015, the value of prescription drug sales would plummet as patents expired and generics entered the market. The reason? Many big pharma companies had failed to come up with enough promising drugs to compensate for the revenue that would soon be lost. Generally, these predictions were very accurate. Over the last 3-5 years we've seen some of the largest products in the history of pharmaceuticals lose their patent protection. The ranks among big pharma companies have changed and business models have had to adapt. The resulting job cuts and other cost-containment measures have hit many companies hard. However, we can now see that the predictions only captured a part of the big picture. While the profitability of many of the old blockbusters has declined, new types of pharma products are taking over, especially within the category of specialty drugs.

The new reality of manufacturing

There has been a lot of discussion about the impact of the patent cliff on drug discovery, development and the general business landscape for our industry, but I think a lot of people forget about another very important topic: manufacturing. It may not be clear to everyone just yet, but the challenges that manufacturers face now are very different to those seen when the patent cliff predictions were made.

Back in the so-called 'blockbuster era' – before the patent cliff – the most profitable drugs were traditional medicines, mostly oral solid dosage drugs for lowering cholesterol, thinning blood and other common indications. They were manufactured in huge quantities, typically in specialized facilities, with technology that has remained largely unchanged for 50 years. Of course, most of these products still exist on the market, but they now have generic competitors. Coupled with pressure from healthcare payers to cut costs, their value has been so eroded that the holders of some of the big brands are even considering selling them off. Many of these former blockbusters are no longer produced in large dedicated facilities by the originator, but are instead farmed

out to contract manufacturers have become part of a much larger portfolio within generic companies.

After the patent cliff, the greatest business value is created by specialty medicines, produced in much smaller quantities. In 2014, products like AbbVie's Humira, Johnson & Johnson's Remicade, Pfizer's Enbrel, Roche/Genentech's Avastin and other specialty medicines are high up on the list of the most profitable drugs. These specialty medicines have a much higher business value per unit than the high earners in the blockbuster era, such as Pfizer's Lipitor, Sanofi/BMS's Plavix or Novartis' Diovan. With some notable exceptions, today's specialty medicines are mostly injectables, which require a totally different manufacturing process and technology than the tablets or capsules of the blockbuster era. Starting as a niche area in most companies, aseptic processing has now taken center stage in manufacturing – and for many companies that is a significant challenge.

To complete the picture of the challenges facing manufacturers in the post-patent cliff world, we must note that the new breed of specialty drugs are often offered in pen systems, pumps or other advanced drug delivery systems. This adds complexity to the facilities – and supply chains – of the future. Aforementioned Humira and Enbrel are offered as pens or easy-to-use pre-filled syringes. And though such systems markedly improve patient convenience and compliance, it means that the pharmaceutical facilities of the future will need to master much higher complexity in the manufacturing processes.

It is not only the business complexity of the supply chain but also the complexity of regulatory compliance that has increased. From a good manufacturing practice (GMP) perspective, the challenges of aseptic processing are profound and there have been a number of significant regulatory actions against aseptic facilities over the last few years. Many aseptic processing facilities are quite old, and new technology, including various forms of barrier technology and advanced containment solutions, are being encouraged by pharmaceutical inspectors to mitigate the risks of aseptic processing. In my opinion, regulatory focus has increased; I have seen a number of regulatory presentations at conferences over the last couple of years, pointing to what the facilities of the future should look like to ensure regulatory compliance.

A bigger picture is beginning to emerge of what the new pharma reality for manufacturers may look like. Volume is no longer the priority. Instead, I foresee scalability, flexibility and safety – or regulatory compliance – 'by design' to be the drivers when manufacturing the medicines of the future.

Value, not volume, drives design

New specialty medicines are costly, even compared with blockbuster drugs at their peak. They are produced in small or medium volumes, but the business risk of manufacturing them is high. Demand is hard to predict, so bottlenecks can easily occur; flexibility is one of the most important factors for success when manufacturing specialty drugs and avoiding shortages. The new blockbusters, such as Biogen Idec's Tecfidera and Gilead's Sovaldi, are setting new records for successful drug market launches, but this is adding significant pressure on the manufacturing organization that has to supply the products.

Most pharma companies have reacted to the patent cliff by streamlining operations and cutting costs, with initiatives in particular focusing on lean manufacturing, six sigma, de-bottlenecking and supply chain management. Manufacturing has been a prime target for rigorous cost-cutting, but many of these measures were designed with the stable production of large volumes in streamlined facilities in mind. They are less effective when volumes are small and flexibility is important. Today, several of the old facilities for some of the biggest products have been sold or are up for sale after the launch of generic competitors.

Pharmaceutical companies require a new combination of cost-effective manufacturing and high flexibility. It is new to the pharmaceutical industry, but the automotive industry faced up to this reality many years ago when it turned from dedicated facilities to flexible manufacturing. From having dedicated manufacturing lines for each car model, the car industry has moved to manufacturing units that make full use of just-in-time principles and high flexibility, even at lower manufacturing costs. Pharma must now make the same shift.

Part of the answer for many companies is to team up with contract manufacturers for some or all of their production volume. Contract manufacturers have flexibility in their DNA – they are often dealing with multiple projects at any time and the tight margins of the business force them to be cost-effective. Besides, they can build an economy of scale by combining manufacturing of similar products from different customers, where possible. Traditional pharma companies could learn a lot from these companies.

"I foresee scalability, flexibility and safety 'by design' to be the drivers of the future."

New technology

Pharmaceutical manufacturing has seen a number of new technologies emerge over the last 10 years: single-use technology for biopharmaceuticals, isolator technology for aseptic processing, and new inspection and sterilization technologies, to mention just a few. Some have the potential to become disruptive innovations, whereas others may exist side-by-side with traditional technologies. When considering new manufacturing technologies, the old dilemma of balancing the initial investment with the cost of manufacturing (including depreciation) is ever present. But there are some solutions now coming onto the market that are relatively cost-effective to implement. As Guillaume Plane discusses in depth on page 24, single-use systems are a good example since they offer benefits in both cost and flexibility. They have seen rapid uptake in biopharmaceutical production and have significantly reduced the cost of new facilities. In aseptic filling, the adoption of ready-to-use syringes and other primary components could reduce filling line complexity by eliminating processes for washing and sterilization. In packaging, in-line printing holds similar potential by eliminating storage, reconciliation and other packaging support activities.

Other new technologies require a higher investment at the outset, but result in more cost-effective processes. Continuous manufacturing is one of these, but adoption has been slow. There are only a few suppliers and the technology is expensive, but with FDA and EMA endorsement and new regulations that facilitate implementation, widespread use may perhaps be in sight. When this technology reaches economy of scale, with its lower requirements on space, handling and batch management, the balance of investment versus operational cost could shift dramatically. It's an exciting time to be re-evaluating manufacturing operations and preparing for the future.

Speed to market

At one point, speed to market was not a major concern for pharma companies. Historically, companies developed predictable decision models based on the approval process and market adoption of new drugs, and these worked very effectively during the reign of the blockbusters. Time to market is now crucial, both from a business and a patient perspective. Several regulatory agencies, most notably the FDA, have established programs and initiatives that can speed up the approval time for so-called 'breakthrough drugs', such as Roche/Genentech's Gazyva or Gilead's Sovaldi. As new drugs that solve unmet needs become more common, pharmaceutical companies will have to re-evaluate their decision-making processes. I expect that we will be facing a new pressure on time-to-market. In this climate, the agility of pharmaceutical manufacturing and fast-track engineering will take on new importance.

Facilities of the future

The drop off the patent cliff period is an opportunity for companies to take a close look at their facilities. Are they using and combining new technologies? Are they cost-effective? Are they flexible enough to cope with changing demands? Are they fit for function in this new reality?

In the facilities being built now, I've seen smaller innovations rather than paradigm shifts, but I'm confident that the breakthrough facilities are coming. Several big pharma companies have announced investments in the US, UK, Germany and India for truly inspiring new solutions, some of which can be seen at www.facilityoftheyear.org. The next couple of years could see the launch of facilities with many of the elements that will constitute pharmaceutical facilities of the future.

Gert Moelgaard is Vice President of Strategic Development at NNE Pharmaplan, Denmark.

The Biomanufacturing Facility of the Future

Times are a changing. The rise of biopharmaceuticals has resulted in the need for cheaper, faster manufacture without a subsequent sacrifice in safety. Here, I offer my vision of how the manufacturing facilities of the future will combine the technologies of today and tomorrow.

By Guillaume Plane

Many new trends in pharmaceutical manufacturing have emerged in recent years as the industry adjusts to the demise of the blockbuster era. As many small-molecule blockbusters have come off-patent and innovation has slowed, the biopharmaceutical industry has flourished, spawning a growing number of drug approvals and new facilities. But despite successes, biopharmaceutical manufacturing has not been entirely untouched by the challenges facing the industry as a whole. As Gert Moelgaard stated, flexibility is likely to be a big driver of the future. Gert examined the broad trends affecting the industry and how we have to change as result. Here, I present an in depth look at the situation in the biomanufacturing space.

Whether manufacturing monoclonal antibodies, hormones or recombinant proteins, drug makers have to develop a 'biological factory' that can be incorporated in a manufacturing facility. The stars of today's biomanufacturing facilities are the bioreactors that are used for cell growth, and the downstream equipment for harvesting, purifying, and concentrating drugs. Many of the current facilities sprang up quickly when the trend towards biopharmaceuticals became apparent, devoting manufacture to just one product to avoid cross-contamination. Today, these facilities are evolving to better match today's new drugs and technological opportunities.

Biologics of the future

It is evident that the biomanufacturing facility of the future will depend on the biopharmaceutical drugs of the future. Currently, more than 3,000 biopharmaceutical drugs have been launched; over 6,000 are in preclinical/discovery stage; and 4,000 are in clinical development (1).

The biggest R&D pipeline – more than 4,000 products – exists in the cancer space. Of course, not all will be filed, but the number of products in oncology is set to increase dramatically. Increased understanding of the complex interplay between genetic, cellular and environmental factors suggests that there may be as many different cancers as there are patients. For example, trastuzumab is an effective drug for treating breast cancer, but only in the 25 percent of patients with tumors that overexpress HER2 (2). The cost to sequence a whole human genome is now less than $1,000 and takes only a few hours. In the future, I believe we'll see sequencing of tumor genomes being used as point-of-care testing, allowing physicians to choose a drug on a molecular basis versus simply a histological analysis. For each new gene and molecular pathway implicated in cancer, there is the potential for a new biologic drug; therefore, not all of the new biopharmaceuticals launched can be blockbusters. Some will only be suitable for a subgroup of cancer patients, and facilities will be needed that can produce small quantities of many different biologics.

Another important trend is the rise of biosimilars. The first synthetic erythropoietin, granulocyte-colony stimulating factor, somatotropin and trastuzumab are all pioneering drugs that have now tumbled off the patent cliff; however, biosimilars are not nearly as straightforward as generic small-molecule drugs to manufacture. The molecular structure of biopharmaceutical drugs is related to the genetic background of the cell line used for biomanufacturing, with post-translational modifications, such as glycosylation, each having an impact. Each cell line is the exclusive property of the company that originated the product, so biosimilar companies have to generate a new cell line for each new biosimilar product they produce. Because the new cell line could be slightly different from the one used for the original product, biosimilar companies have to present results of toxicological studies and clinical double-blinded studies to prove that their biosimilar product is truly similar to the originator.

From a marketing standpoint, once a biosimilar drug receives market approval it must also differentiate itself from the competition. For generic or biosimilar drugs, price is the main differentiator. As a consequence, if the price of the originator biopharmaceutical decreases, then so too must the biosimilar, despite expenditures in clinical and toxicological studies. This is one reason why there is great pressure to reduce costs in the biomanufacturing area.

The sometimes-dramatic differences in the costs of biologics was highlighted recently by the case of anti-vascular endothelial growth factor (VEGF) to treat age-related macular degeneration (AMD). Ranibizumab is a monoclonal antibody targeting VEGF for the treatment of AMD. Its end-user price is $2,000 per month. Bevacizumab is a similar molecule, also targeting VEGF, but its indication is for the treatment of cancers. Its end-user price is less than $50. Such disparity has bewildered the public. From an industry perspective, the price of a drug must not only cover the cost of manufacture but also the risks and costs of innovative development. But the public is not ready to accept that there can be a 40-fold price difference

in virtually identical products, both of which are profitable. Pressure from governmental authorities and patient associations is strong, and this is translating into increased pressure on costs. The biomanufacturing facilities that will survive in the future are those that that can help contain costs with increased flexibility and better yields.

Disposable flexibility

As Gert mentioned on page 23, a key trend in bio/pharma manufacturing is the uptake of single-use systems. Single-use systems are generally comprised of hardware and disposable components – the hardware carries the tools related to the biomanufacturing step, such as motors of mixing systems; and the disposable component is single-use, for example, bags where buffers can be mixed.

When using disposables, bioreactors are no longer rigid stainless steel tanks with welded pipes for adding cell culture media or buffers, with sensors that are difficult to calibrate and qualify. Processing after harvesting in stainless steel tubes that have to be washed, sterilized and qualified after each batch is also a procedure of the past. Disposable systems mean that we can produce a drug in plastic bags and pipes that don't require washing, sterilization or validation. I believe it won't be long before we can say, "goodbye" to glass and stainless steel for clinical – and even commercial-scale biomanufacturing.

From an ecological standpoint, the first impression may be that single-use systems are a backward step, since they are plastic and wasted after production. However, first impressions can be misleading – using disposables eliminates the use of thousands of liters of ultra-pure water usually required for cleaning. It also reduces the corresponding effluent discharge and subsequent pollution. As a result, the ecological equation is in fact thought to be in favor of disposable equipment (3).

The advantages of single-use equipment are attractive for one product, but for the production of multiple products become even more evident. In the past, each stainless steel biomanufacturing facility was used for one single product to avoid cross-contamination inside the tank. Single-use tanks can be discarded after production and replaced by another system, allowing several products to be produced in the same area, one after another. Another reason why facilities were devoted to one product in the past is that tanks and equipment had to be specific to the product. For example, consider the equipment required for downstream processing if the yield of the upstream step is 1 g per liter versus 6 g per liter. The size of the tanks, capacity of the chromatography columns and surface of the filters will be different. As you can imagine, it's tricky to replace a 500 liter tank with a 2,000 liter tank quickly in a stainless steel facility where tanks are linked to others by welds. These bottlenecks are avoided with single-use systems.

Despite the advantages of disposable manufacturing, we currently don't have the technology to use it in every process step for biomanufacturing. Purification steps, for example, cannot be handled with disposable equipment because chromatography resins are too expensive to use only once, especially the protein A resin that is required for purifying antibodies. Pre-packed disposable columns do exist at pilot scale, but even if they are developed for process scale, they will not be handled as single-use equipment. Unless we can find a new, cheaper purification membrane that can capture antibodies as efficiently as protein A – a tall order but a clear area crying out for innovation – this is likely to be the case for many years to come.

As a consequence, our biomanufacturing facility of the future will be able to produce several different products, but will use both stainless steel and single-use technology. I envisage it as a puzzle, where disposable pieces can be assembled to

fit with the requirements of the production process of a given biopharmaceutical product. The puzzle can then be disassembled and reassembled when a new product requires a different configuration.

Quality control

Single-use systems represent a big change in the way manufacturers handle quality issues. The plastic bags have to be considered as expendables, while the hardware component of the disposable system is subject to Installation and Operation Qualifications (IQ/OQ). The providers of the plastic bags must be qualified by manufacturers from a logistical and quality standpoint, and traceability has to be in place. The plastic composition of the bags also has to be under control to avoid any issues, as the drug substance is in contact with it during processing.

Indeed, the question of extractables and leachables is something that is becoming a hot topic in biomanufacturing. Does the plastic release any particles when in contact with water? Does it release any particles when in contact with cell culture media, buffers and drug substances during manufacturing? Could any of the leachables be dangerous for patients when the drug is injected? Some consider these inquiries secondary questions, given that blood for transfusions has been stored in plastic bags for decades. However, the recent case of bisphenol A in baby bottles shows that extractables and leachables are certainly critical in healthcare. Plastics generate extractables and leachables, and it is the responsibility of the manufacturer to show that these particles are not dangerous for patients.

Today, the best technique to analyze extractables and leachables is mass spectroscopy, which can identify and quantify contaminant material. Analysis can be performed on plastics when water is processed in bags, when cell culture media and buffers are processed, with or without cell culture, with or without drug product, to ensure a good control of these particles during and after processing. Clearly, the biomanufacturing facility of the future would need to be equipped with state-of-the-art analytical quality control technology.

> *"Continuous processing is another trend that is much more oriented to yield improvement and cost containment during the upstream steps."*

Fully closed and continuous processing

The way we use the above operational units will be another driver to increase yields and thus reduce cost of goods in the facility of the future. To that end, a big trend is emerging: fully closed processes and continuous processing.

The main reason for fully closed processes is to avoid contamination during processing. From thawing of the cell

Towards Continuous Manufacture

Insight from Bernhardt Trout, Director & Principal Investigator, Novartis-MIT Center for Continuous Manufacturing

What are the benefits of continuous manufacturing?

Continuous manufacture, as we define it, is very much about achieving the ultimate process understanding, the ultimate process efficiency, and the ultimate product quality. The idea is not just to take existing technology and run it continuously, but to develop new technology. The aim is to develop a fully integrated process, including an integrated control system. The whole process is streamlined – it is more efficient, with reduced throughput times, smaller facilities and decreased costs, and quality is improved by avoiding potential issues with sterility and variation between batches.

What are the main barriers to implementation?

One potential barrier is the investment required to develop new technology. Another barrier, or at least perceived barrier, is regulatory approval for this new process. But I would say the number one issue is mindset. It's a very conservative industry that can be reluctant to do things in a completely different way. Pharmaceutical manufacturing is lagging behind other areas, such as automotive and electronics

line devoted to the production of one given drug substance, to the fill and finish step of this product, contamination can be limited if the cells and the product are never in contact with the outside environment. Disposable bags and pipes can now be designed to allow closed processing, from the working cell bank to the final tube containing the product.

Continuous processing is another trend that is much more oriented to yield improvement and cost containment during the upstream steps. Instead of producing one batch with one cell culture that will be harvested once, the cell culture can be continuously supplied with cell culture media, and continuously harvested without stopping the culture, thanks to proper filtration and loops on the flow. This allows the production of more cells – and thus molecules – at the same time, as the culture continuously runs at high density and consequently at high yield (see sidebar, Towards Continuous Manufacture).

Local knowledge

When imagining the biomanufacturing facility of the future, we shouldn't forget sociological and economic trends. The environment and global warming, for example, are becoming more important issues for many. The public don't understand why a drug has to be produced 20,000 km away, shipped to their country in a temperature-controlled box, with very high margins, when production could be handled locally instead, benefitting both the environment and providing local jobs. Of course, this is not limited to the pharmaceutical industry. President Obama wants American companies to bring jobs back to America. The same trend can be seen in Europe, especially in France.

As a consequence, even now there is a trend to build regional facilities. I fully expect that this will continue – and evolve. Instead of building large global manufacturing facilities for just one product, companies will build smaller facilities capable of manufacturing several products for regional sales. And in fact, regional manufacture is also beneficial from a regulatory standpoint, as expectations can vary from one country to another, despite harmonization efforts.

To conclude, economic and political trends will push companies to establish regional facilities where they manufacture several products for local markets, while pressure on costs will ease as greater flexibility allows optimal management of the workload. The biomanufacturing facility of the future will be like a giant Lego set; operational units, such as bioreactors, clarification systems, tangential flow filtration systems, purification and chromatography systems, will form the pieces, with pharmaceutical 'players' easily assembling, disassembling, and reassembling them to create any product, in any amount, at any time.

Guillaume Plane is Global Development & Marketing Manager at EMD Millipore, France.

References

1. *BioPlan Associates , "11th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production" (2014).*
2. *European Medicines Agency, "Herceptin", EMA/981900/2011 (2011)*
3. *M. Pietrzykowski et al. "An Environmental Life Cycle Assessment Comparing Single-Use and Conventional Process Technology", BioPharm International Supplements, s30–s38 (2011).*

manufacturing. There is a lot of inertia – of organizations, of procedures and of thought. As we know from Newton, to change an inert system, we have to apply force! That force has to come from top management. They have to be willing to invest and make the organizational changes required. Here, the biopharmaceutical industry has an advantage over small molecule drugs – as a newer industry, they are more open to newer technologies, but still suffer from the above problems.

How soon do you expect to see significant uptake of continuous processing?

It's been slow but steady. Novartis is the leader in terms of investment in R&D for continuous manufacturing and in terms of timing. Their focus is on small molecules, but the overall concept follows through to biologics. Genzyme, part of Sanofi, has been working on biocontinuous processing for some time. I think it will gradually increase, until the point where one company launches a fully validated, working continuous process – after that I think it will accelerate rapidly.

What other trends do you hope to see in pharma manufacturing in the future?

Here at MIT, we do a lot of outreach – both with the industry and with the public. We think it's important for everyone to have a clear understanding of pharmaceutical manufacturing and its importance. When we think of automobile manufacturing we can envisage assembly lines and robotics, but few people easily envisage pharmaceutical manufacture. In the future, I hope to see a much stronger understanding of pharmaceutical manufacture, both for upper management – many of whom don't have pharmaceutical manufacturing backgrounds – and the public as a whole.

eppendorf

Highly Scalable

Eppendorf for Bioprocess – Solutions that grow with you

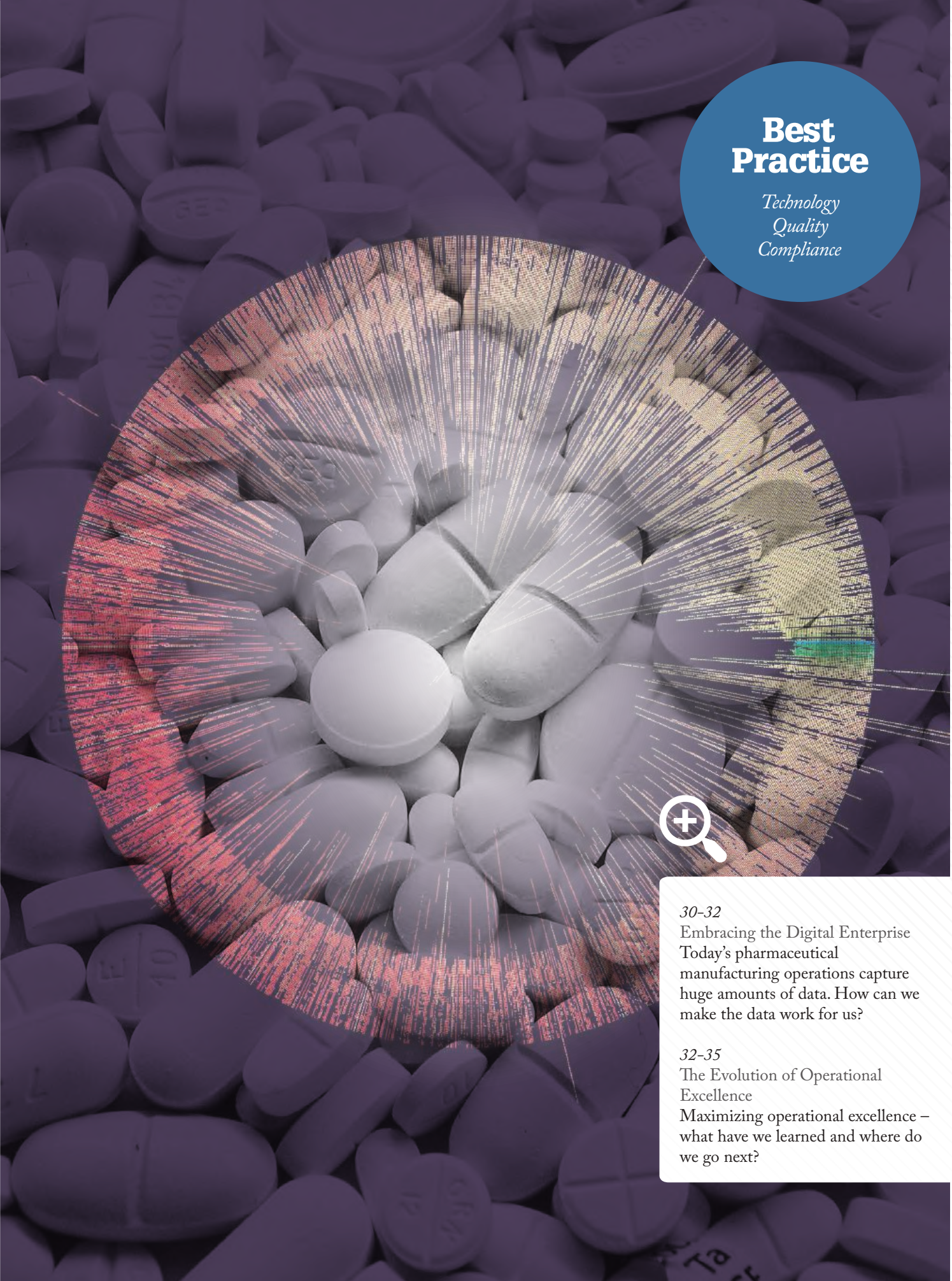
With renowned expertise in plastics manufacturing, Eppendorf is proud to offer scalable single-use vessels to be operated with the DASbox® parallel mini bioreactors system, DASGIP® Parallel Bioreactor Systems or New Brunswick™ CelliGen® BLU controllers.

- > Proven for animal and human cell lines as well as bacteria and yeast
- > Working volumes of 100 mL – 40 L in cell culture and 65 – 250 mL for microbial application
- > User-friendly set-up for shorter development times and lower operating costs

www.eppendorf.com

Best Practice

Technology
Quality
Compliance



Embracing the Digital Enterprise

Today's pharmaceutical manufacturing operations capture huge amounts of data. Unfortunately, in many cases the data pass by without actual context. How do we obtain the digital "Holy Grail" – a fully mapped process that facilitates decision-making using data we trust?

By Bob Dvorak, PhD & Rick Johnston, PhD

We recently visited the process development group of a large pharmaceutical company with a colleague to gather information about process analytical technology. We asked the head of the group to describe some of his challenges around data. He repeated the well-worn refrains heard in many companies: old technologies and lack of integration. Then he said something that stuck with us: "I feel like I am looking through a knothole in a fence, watching my data go by. There is no way to understand the upstream and downstream context or to interact with it."

This is exactly the problem with most data strategies in bio/pharma manufacturing; though they typically show specific data with absolute clarity, the context and connection for the data to be truly useful is missing.

Today, the biopharmaceutical industry captures massive amounts of data about its products and the processes that allow them through its well-established automation systems, data historians, document controls and manufacturing analysis systems. Each of these is an 'island of data' that is integrated as and when needed to ensure execution continuity. This point-to-point integration is OK for many of these systems since it solves the short-term goal of manufacturing product, but does little to address the broader questions that a decision-maker may have:

- Where are the critical places in the process that are the least robust?
- How much is this downtime costing us?
- How much material should I make based on current demand?
- Which of my plants is currently making this product most efficiently? And why?

The lack of a central source of process context leads to data gaps about the overall manufacturing process.

When 'something' (a problem or unexpected event) occurs in the process, those data gaps result in an inevitable meeting request in your calendar. People who understand the process are brought together and data from multiple sources is reviewed and queried. The hope is that the individuals in the room will somehow recognize the data they are watching and be able to make sense of it in terms of the process. In fact, each expert is "looking through the knothole" at data, seeing specific pieces of information without understanding them in a broader context. Having enough eyes on the problem can make it possible to find patterns, but that means the involvement of many people every time a problem occurs. And even then you may not always be able to spot the issue. There is a better way.

Adding digital context

We have to change the way we think about data. Importantly, we must close the gaps that exist between the traditional 'islands of data' and instead focus on creating a richer context for our process data. This context is captured not just in a series of meetings, but in a formal model of the manufacturing process that tracks relationships, business rules, equipment and resources. This model is designed by the subject matter experts who understand the process, and their meetings should occur long before 'something' happens. These experts can build the process, identify the key data that needs to be collected, and visualize that process directly.

The approach also avoids unnecessary customization of the system and ad-hoc queries (which encourage rigid business processes) and instead focuses effort, data and automation in the areas that need it the most. We call such an effort the digital enterprise.

A central driver of the digital enterprise is better and faster decision-making. Whether to better embed quality into the process (Quality by Design) or enable continuous improvement, data needs context, which must be based on sound process understanding. The digital enterprise builds on the automation systems you already have in place and allows users to see how a change in one area of the facility cascades through other processes and areas via a complex set of relationships and business rules. Identifying the pattern of cause and effect up front enables the business to see the impact of a change or adverse event not just on a single manufacturing area, but on overall metrics like adherence to plan and cost per batch.

The foundation of the digital enterprise starts with capturing your process knowledge to create an overall 'map' of the process that provides context for data. The map gets populated with data from your manufacturing runs, with knowledge from your experts and, coupled with your historical data, provides a foundation of certainty about what you will be seeing. This approach allows you to tunnel into the unit operations in a meaningful way: not mining data, but populating process models with actual numbers.

Accuracy and logic are needed to correctly model the dynamics of the system being studied, which requires a formal methodology. For example, Schruben's model accreditation protocol can be used to ensure that the model is an accurate reflection of plant operations. This model relies on the judgments of a team of experts who need to distinguish simulated system performance from actual system performance. The experts must then use deep process knowledge and experience of many batches or experimental runs to refine the models and create the basis for confidence in the data.

Shifting the lens

We are all familiar with the current 'big data' trend - analyzing massive datasets for trends that can be used to the organization's advantage. The challenges of 'big data' arise when the data sets are external, uncontrolled and unstructured, and must be gathered and processed. In manufacturing, that data is created and structured by you, so an understanding of the decisions you want to make should drive your data strategy.

In the old model of data analytics, the 'lens' of analysis is only typically applied when a decision needs to be made (Figure 1). Data is collected and brought together in a painstaking manual process. At each stage, individuals attempt to 'strip down' the quantity of information into manageable streams that can be understood. That information is interrogated to turn it into knowledge that can be used to make a decision. While this traditional approach does (eventually) get decisions made, the transformation of data into information into knowledge usually requires active work, for example, looking at reports and interpreting them.

However, since knowledge only has value to the organization when it enables actionable decisions, the next step must be to look at how decisions themselves are managed. Modern manufacturing intelligence systems should model the knowledge you have about your products, processes, and resources. Then they should gather data from the fully digitized enterprise that provides current information (Figure 2).

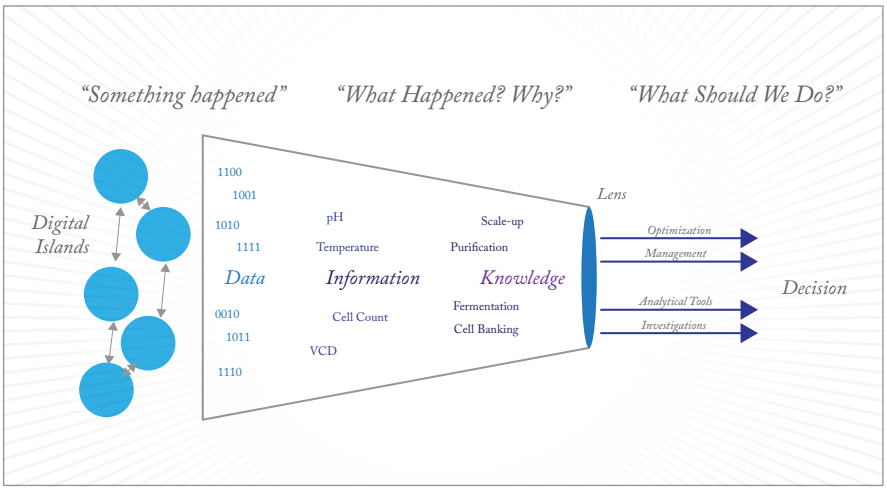


Figure 1. The old model of data analytics

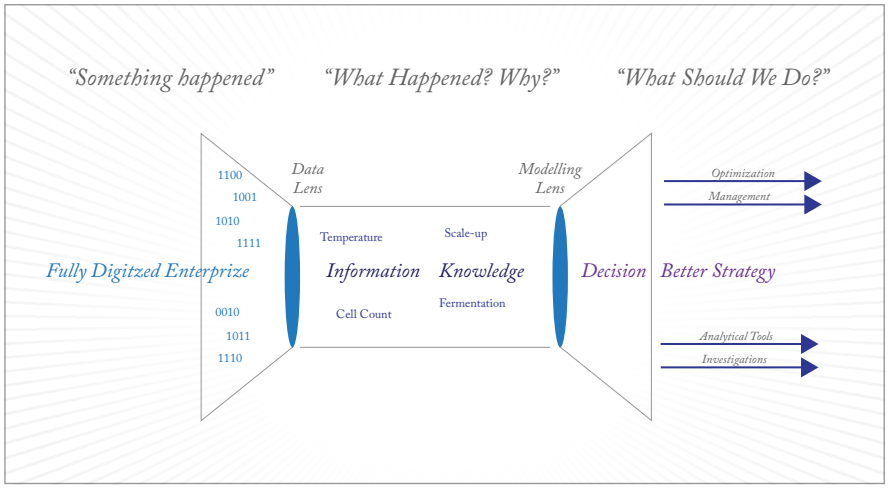


Figure 2: The fully digital enterprise

This concept transforms the way we look at data. Knowledge isn't pulled from information: it is modeled on an understanding of the way we manufacture the product. Information isn't extracted from data: it is the way that data is structured. Now, the lens of analysis moves right up to the data itself. It is not the 'knothole in the fence' through which data is observed, but the real-time measure of a well-understood process – placed in a context or map of that process. Data becomes a snapshot of performance rather than something to be translated.

The real power to your organization comes when both the operator at the terminal and the manager on the floor have a device, such as a smartphone or tablet, that provides an instant view of data in a format familiar to them. With that process visualization, events can be addressed immediately and decisions can be made with minimal delay. The ability to go beyond individual events and to instead see trends helps to make those decisions progressively smarter. The more knowledge grows, the more decisions are informed and vetted. A key element is the certainty that the decision is being based on a full picture, with the complete context well-defined. When 'something' happens, it is an anticipated event.

The Digital Enterprise: Defined

- All business processes captured in digital systems.
- Data modeled on the business process.
- No gaps in the flow of data between elements of the business.
- Visualization tools that show data in real-time and in context.
- Mobile and workstation access to data in the context of the operator or supervisor viewing the data.
- Combined data views of how things should work, how they are working, and what this means for the profitability of the business.
- Fast decision-making, based on data you trust to be complete and accurate.

Escaping 'average'

Ultimately, the real power of the digital enterprise comes from managing the ordinary variations that occur in bioprocessing. The digital enterprise, based on the model of the process, allows us to escape the fallacies that arise from the law of averages. Think about a bioprocessing plant like a drunken man walking down the middle of a busy road. He staggers right and left, but on average, he is walking the median. In the theoretical model, he makes his way safely along the road and stays alive. In practice, he wanders off the median and gets hit. He is dead in practice.

Older models have to focus on the 'average' batch because they lack the defined process and complete data set to actually track the variations. In the digital enterprise, you can predict based on the past, react based on the present, and get smarter in the future. Systems can react to the anticipated event. People can react to the unanticipated event with immediate visualization of the data they need to make their decisions. Then those decisions become part of the overall knowledge base and that unanticipated event becomes an anticipated one.

Total disruption of the current 'Islands of Data' approach is critical. Those islands must be connected together by interfaces and reports to obtain a fully mapped process that enables rapid decision-making based on data that you trust – that's the 'Holy Grail'!

When Indiana Jones goes through his trials to reach the 'Holy Grail', he has to take a leap from the lion's head – a leap of faith. He sees the chasm in front of him and he knows he must continue. And yet there is no way he can clear the gap. He closes his eyes, takes a deep breath, and then takes a step forward and finds that he is on solid rock. No leap was required because the gap never really existed. The digital enterprise is about having your team step onto solid rock instead of making some wild leap across the chasm of data.

Bob Dvorak, PhD is Principal at BioPharma Data & Manufacturing Systems Consulting, San Francisco Bay area and Rick Johnston, PhD is founder and CEO of Bioproduction Group, Berkeley, CA, USA.

The Evolution of Operational Excellence

In today's competitive market, OPEX is – or at least should be – a priority for all pharmaceutical manufacturers. Looking back on just a decade of progress, what have we learned and where do we go next?

By Thomas Friedli, Christian Mänder and Prabir Basu

The history of operational excellence (OPEX) in the pharmaceutical industry is short; the first serious OPEX initiatives were only launched about 10 years ago. Before that, the pharmaceutical industry was reluctant to put OPEX and continuous improvement on its agenda, in part because of the regulatory environment but also because it was not suffering from the same cost pressures facing other industries, such as the automotive and electronics sectors, which were forced to adopt OPEX earlier.

The discussion about a more scientific approach to pharmaceutical manufacturing only really began at a US FDA scientific advisory board meeting towards the end of 2001. The agency was facing an increasing number of post-approval manufacturing amendments at the time, making it tough to fulfill their review and inspection obligations. It became apparent that the industry did not truly understand its own manufacturing processes and that there were gaps in the science needed to gain useful knowledge. Current good manufacturing practices (cGMP) were being driven more by experience than sound science, which raised concerns, as did the overly risk-averse nature of industry and regulators.

At the same meeting, Doug Dean and Francis Brutton from PriceWaterhouseCoopers presented

a rather bleak analysis of the status of pharmaceutical manufacturing and identified the root causes:

- Processes that were neither fully understood nor suitable for commercial scale were being transferred from the laboratory to manufacturing.
- Lengthy and elaborate new product introduction exercises generated data but failed to provide critical information.
- 50 percent of production costs were locked in before Phase III had begun.
- Process inefficiencies were "institutionalized"; companies were reluctant to put in the time to gain deeper process understanding.

Both the industry and the FDA were well aware of the deficiencies in pharmaceutical manufacturing, and knew that to move forward they must encourage the use of innovative technologies to enhance process understanding and establish scientific, risk-based approaches to quality and regulatory processes. The FDA and the industry assembled a process analytical technology (PAT) Team to evaluate how they could further promote this concept. The PAT Team and Manufacturing Science Working Group agreed that things had to change:

"Pharmaceutical manufacturing operations are inefficient and costly. The cost of low efficiency is generally not understood or appreciated (e.g., manufacturing costs far exceed those for research and development operations). Low efficiency is predominantly due to 'self-imposed' constraints in the system (e.g., static manufacturing processes, focus on testing as opposed to quality by design, approach to specifications based on discrete or the so called 'zero tolerance' criteria, a less than optimal understanding of variability, etc.). These constraints keep the system in a corrective action mode. Continuous improvement is an essential element in a modern quality system and it aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. In the current system continuous improvement is difficult, if not impossible (1)."

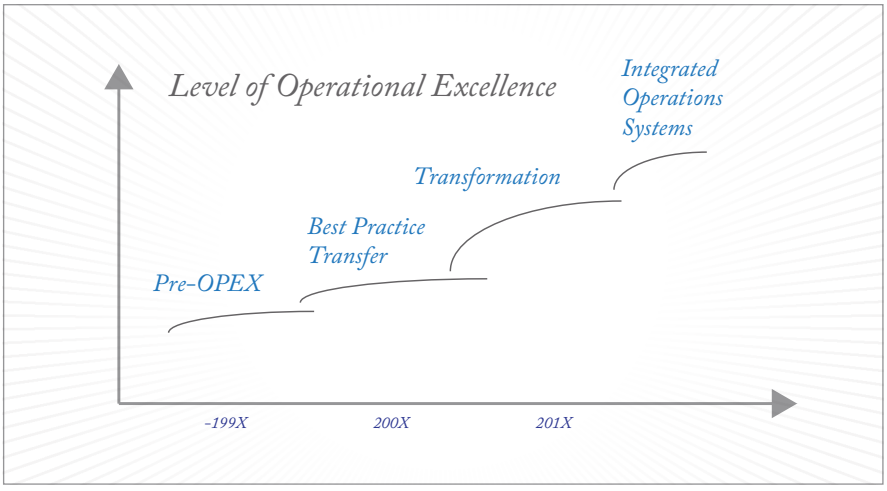


Figure 1. Pathway to operational excellence in the pharmaceutical industry

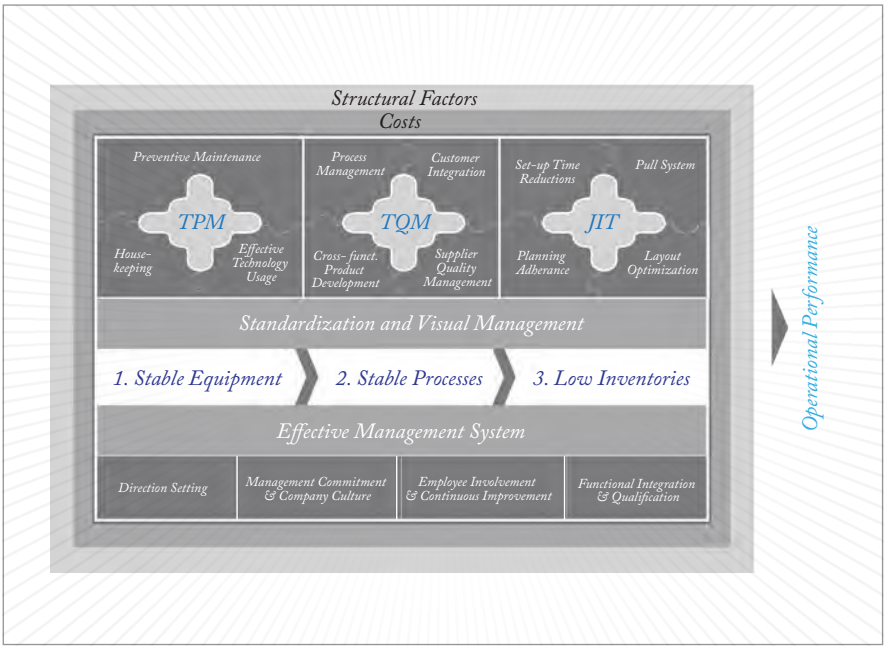


Figure 2: Structure of the St. Gallen operational excellence model. (TPM: total productive maintenance, TQM: technical quality management, and JIT: just-in-time)

In response, the FDA shifted from its position of focusing on product purity and potency as its measure of quality, towards a regime that focused on the actual physical manufacturing processes (2). The idea was that a more thorough understanding of the processes would lead to more predictable and efficient manufacturing. In August 2002, the FDA announced a significant and bold initiative: Pharmaceutical cGMPs for the 21st Century. The aim was to encourage the early adoption of new technological advances by the pharmaceutical industry, to base regulatory review and inspection policies on state-of-the-art pharmaceutical science, and to facilitate the use of modern quality management systems. Risk-based approaches would focus both industry and agency attention on critical areas and incorporate enhanced quality system approaches into the agency's business processes (3).

The FDA also gave details of what it

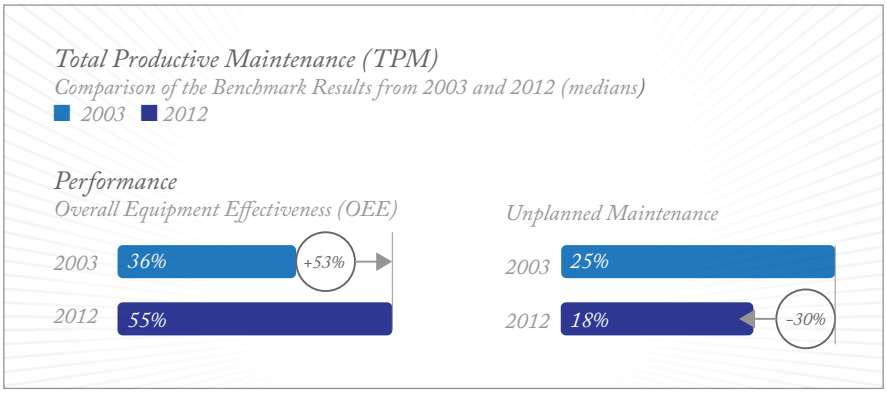


Figure 3: Performance improvements in total productive maintenance (8).

termed the "desired state" – its vision for pharmaceutical manufacturing:

- Product quality and performance assured by design of effective and efficient manufacturing processes.
- Product specifications based on mechanistic understanding of how formulation and process factors impact performance.
- Continuous improvement approaches, with innovative use of new technology as desired.

Subsequent FDA activities were all based on the same underlying idea: to modernize the science base for pharmaceutical manufacturing and quality management (4).

OPEX evolution

Comparing today's management of OPEX with the first early efforts, we can distinguish three evolutionary steps (see Figure 1). First, there was the "Pre-OPEX" phase that lasted until the late 1990s. Next came the learning – or "Best-Practice Transfer" – phase, which gave way to today's "Transformation" phase. Looking towards the future, we hope to see the rise of a fourth phase: "Integrated Operations Systems," where we move forward from simply using the tools of OPEX, by integrating the concepts into all aspects of manufacturing – and beyond (5). In our opinion, some pharmaceutical companies that use advanced OPEX programs are already on the threshold of entering the fourth phase – but they certainly didn't get there overnight. Pharma companies currently launching programs can benefit from these experiences and essentially skip straight to the transformational phase.

Pre-OPEX: it's all about cGMP

In the late 1990s, pharmaceutical production was determined by one central force: the regulatory framework, predominantly based on cGMP guidelines. While compliance and finished product quality were the credo of pharmaceutical manufacturing, other practices to improve efficiency and flow were deemed irrelevant to or even incompatible with cGMP. The final product quality might well be excellent, but it was not based on well-understood and efficient processes (6). In fact, pharmaceutical manufacturing was characterized by a high number of rejected batches, lengthy laboratory tests, an extraordinarily high number of inspections and slow feedback loops for subsequent batches (5).

Best Practice Transfer: isolated OPEX applications

At the beginning of 2000, increasing cost pressure, the awareness of inefficiencies in the manufacturing area and the aforementioned regulatory initiatives prompted individual manufacturing sites to start experimenting with performance improvement tools, mostly originating from programs such as Six Sigma, Lean or Technical Performance Measurement. The main purpose was to increase efficiency by "doing things right first time". This OPEX phase is characterized by individual projects dealing with specific tools and practices, guided by experts or external consultants (5). The focus was on tools, not people.

Transformation: company-wide initiatives and programs

What became obvious during the best practice transfer stage was that ideas often stalled, leading to missed opportunities. The approach was too technical and neglected the impact of the people involved in the processes. What was needed? Well, active engagement from top management, changes to the organizational setup and a change management program that actively engaged every single worker in the plant. With these missing pieces in place, sustainable implementation of pharmaceutical OPEX programs was finally possible.

Integrated Operations System: beyond the tools

How can companies reach the fourth and final stage of OPEX evolution? We believe there are a number of crucial aspects (5):

- The many different initiatives in leading pharmaceutical companies should be bundled into an umbrella program, aligning all key activities for improvement of operational competitiveness.
- New and improved practices will be developed and implemented. These practices will be generated internally, so they will rely on effective sharing of knowledge across the organization.
- OPEX will not be limited to practices and standard routines. The mindset to affect change and make

improvements should prevail on all levels of the company.
- OPEX and performance should be seen in a wider context, and not be confined to the boundaries of an organization.
- OPEX will be integrated with quality management. The modern approach to quality is systems oriented, just like the OPEX program. Therefore, a properly planned and executed OPEX program should also be a measure of the effectiveness of the quality systems. On the other hand, overzealous OPEX programs could negatively impact quality. Finding a way to tackle this challenge is one of our key areas of research right now. In the future, OPEX and quality will not be two separate discussions.

Measuring the impact of OPEX

At the Institute of Technology Management at the University of St. Gallen, we assess the impact of OPEX using St. Gallen OPEX Benchmarking to show the individual performance of pharmaceutical production sites. Today, we have more than 270 pharmaceutical manufacturing sites from around 100 different companies in our database.

Figure 2 gives an overview of the key elements in our Operational Excellence Benchmarking model. It measures performance by using production-specific key performance indicators (KPIs) that are closely linked to the technical sub-system (total productive maintenance (TPM), technical quality management (TQM) and just-in-time (JIT)) and the effective management system. With its focus on achieving the goal of "one-piece flow" and minimal buffer inventory, the JIT concept requires stable and robust processes. TQM complements JIT by creating a less variable and more stable manufacturing process that, in turn, reduces the need for safety stock buffers. In mass production, the breakdown of a machine usually does not create a sense of urgency; the maintenance department is scheduled to fix it while inventory keeps operations running. However, in a JIT environment, equipment breakdowns will soon lead to production downtimes. Hence, the concept of TPM, in which everyone learns how to clean, inspect and maintain equipment, becomes a crucial element of a truly excellent production environment (see Figure 3). You cannot build a stable process based on unstable equipment. Figure 2 also shows some key factors for success of the underlying effective management system, with a short summary of the relevant indicators from the St. Gallen OPEX benchmarking (7).

Our benchmark shows an improvement in performance over the last 10 years in both effectiveness and efficiency. For example, looking at TPM, we saw a 53 percent increase in overall equipment effectiveness and a 30 percent decrease in unplanned maintenance between 2003 and 2012 (8).

Another positive finding from our benchmarking is that the number of KPIs that companies are able to measure has increased significantly during the past year. Today, most companies can deliver every KPI we request in our benchmarking questionnaire. Clearly, pharmaceutical companies are thinking more about how to continuously enforce their OPEX activities and create a culture of continuous improvement within their organization.

OPEX is one of the most significant developments in pharmaceutical manufacturing in the last decade. The obvious benefits – streamlining processes and cutting costs – mean that increasing numbers of companies around the world are embracing OPEX. But there are a host of less obvious benefits too: a culture of continuous improvement, teamwork, employee involvement, and a process and systems approach to problem solving, to name just a few. Successful OPEX programs not only improve manufacturing by reducing defects and saving cost, but in the long-run also have an enormous impact on drug quality.

Thomas Friedli is associate professor of management and Christian Mänder is a research associate, both at the Institute of Technology Management, University of St. Gallen, Switzerland. Prabir Basu is a consultant on pharma manufacturing, OPEX and cGMP, IL, USA.

References

1. *FDA, "The PAT Team and Manufacturing Science Working Group Report: A Summary of Learning, Contributions and Proposed Next Steps for Moving towards the 'Desired State' of Pharmaceutical Manufacturing in the 21st Century" (2004).*
2. *G. Clark, "FDA's PAT initiative", Pharm. Tech. Europe 16 (10), 34 (2004).*
3. *FDA, Final Report "Pharmaceutical CGMPs for the 21st Century – A Risk-Based Approach" (2004).*
4. *T. Friedli and J. Werani, "The History of OPEX in the Pharmaceutical Industry", Leading Pharmaceutical Operational Excellence - Outstanding Practices and Cases, s27-34 (Springer Verlag, Berlin, 2013).*
5. *T. Gronauer, T. Friedli, and M. Goetzfried, "The Roadmap to Operational Excellence: Pattern and Elements of OPEX Programs", The Pathway to Operational Excellence in the Pharmaceutical Industry - Overcoming the Internal Inertia, s175-199 (Cantor Verlag, Aulendorf, 2010).*
6. *P. Basu, "The Future of Pharmaceutical Manufacturing: QbD & OE re-inforcing one another", The Pathway to Operational Excellence in the Pharmaceutical Industry - Overcoming the Internal Inertia, p. 324 (Cantor Verlag, Aulendorf, 2010).*
7. *T. Friedli and D. Bellm, "OPEX: A Definition", Leading Pharmaceutical Operational Excellence - Outstanding Practices and Cases, s7-26 (Springer Verlag, Berlin, 2013).*
8. *T. Friedli, N. Lembke, U. Schneider, S. Gütter: The Current State of Operational Excellence Implementation:10 Years of Benchmarking. In: Leading Pharmaceutical Operational Excellence - Outstanding Practices and Cases. Berlin : Springer Verlag, 2013, S. 35-58*

TOSOH

25 YEARS TOSOH BIOSCIENCE

YOUR SPECIALIST IN SEPARATION

YOUR TOOLBOX FOR MAB PURIFICATION AND ANALYSIS

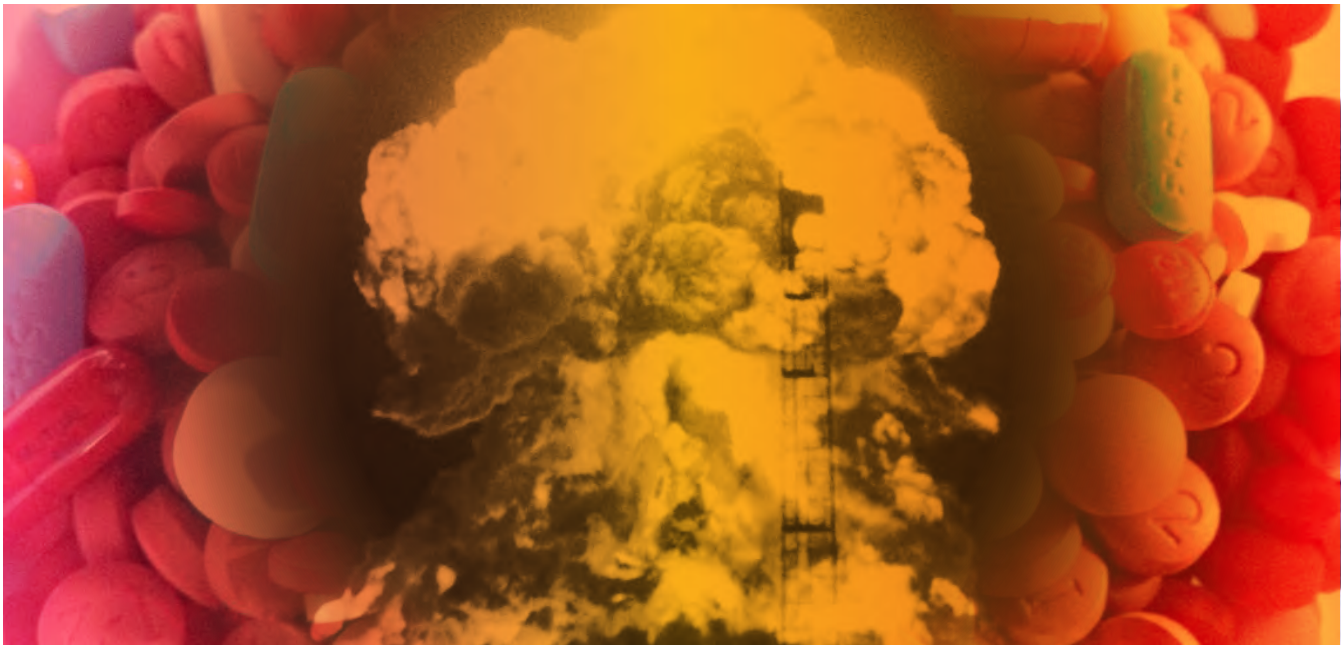
- EFFICIENT PURIFICATION WITH TOYOPEARL AF-rPROTEIN A HC
- FAST CHARGE VARIANT SEPARATION WITH TSKgel STAT SERIES
- HIGH CAPACITY IEC, MIXED-MODE, AND HIC MEDIA
- AGGREGATION ANALYSIS WITH TSKgel SuperSW mAb

CHECK OUT OUR CLIPS ON MAB PURIFICATION AND QC ANALYSIS ON WWW.YOUTUBE.COM/USER/TOSOHBIOSCIENCEGMBH OR FIND OUT MORE ABOUT OUR SOLUTIONS FOR BIOPURIFICATION AND (U)HPLC ANALYSIS ON WWW.TOSOHBIOSCIENCE.DE

TOSOH BIOSCIENCE

NextGen

R&D pipeline
New technology
Future trends



Antibiotic Apocalypse: Part I

Antibiotics were once hailed as wonder drugs in the war against infection, but now it looks like bacteria might have the upper hand. How can we turn the tide?

By Stephanie Sutton

The World Health Organization (WHO) recently described antibiotic resistance as a threat to the achievements of modern medicine. "A post-antibiotic era – in which common infections and minor injuries can kill – far from being an apocalyptic fantasy, is instead a very real possibility for the 21st Century," the WHO explained, as it released its Antimicrobial Resistance Global report on Surveillance in April of this year (1).

The industry has been aware of the growing issue of drug resistant bacteria for some time. In Europe, for example, 'The Microbial Threat' conference, held in Copenhagen in 1998, encouraged a number of EU companies to establish national surveillance of microorganisms resistant to antibiotics. This was also the first time that antibiotic resistance became an official EU issue, although before then the European Commission had tried to address the problem through various isolated measures (2).

The good news is that governments and drug makers alike are taking the problem very seriously. This year, as of September 2014, the FDA had approved three new antibiotics and we've also seen companies such as Roche returning to antibiotic R&D. Many governments are also paying close attention to the problem, which is leading to new incentives and initiatives to help pharma companies get to work – and the recent comments from the WHO are likely to inspire further efforts in the search for the next generation of antibiotic medicines.

Here, I review progress so far and explore the next generation of initiatives from both governments and non-governmental organizations designed to kick-start antibiotic development.

Resistance is not so futile

When antibiotics first came into widespread use around 70 years ago, they were viewed as wonder drugs against infection. However, Alexander Fleming, who accidentally discovered penicillin in 1928, warned of bacteria's ability to become resistant to antibiotics in his Nobel Prize speech in 1945.

Bacterial pathogens have to adapt to survive and evade their host's immune response. Drug resistance occurs naturally through genetic mutations or by acquiring resistance from another bacterium through conjugation, where genetic material is transferred from one bacterium to another. Inappropriate use of antibiotics has accelerated the natural selection of bacteria, which have adapted accordingly and resulted in many multi-drug resistant (MDR) pathogens – or 'superbugs'.

Up until the 1970s, there was a huge amount of discovery and development activity, resulting in dozens of different

antibacterial classes. Since then, the antibiotic landscape has been largely stagnant while bacteria have continued to evolve. According to the WHO, very high rates of resistance have been observed in bacteria causing common infections in all regions. Around 3.6 percent of new global TB cases and 20.2 percent of previously treated TB cases are estimated to be MDR. We've also seen the emergence of extensively drug resistant (XDR)-TB, which is resistant to most traditionally effective treatments (1). A few new classes of antibiotics have been launched since 2000, but most have only one drug within them.

Finding new antibiotics is not easy; the low-hanging fruit have already been picked and bacteria are well equipped for survival. Often, killing the bacteria is not the problem for researchers – it's accomplishing that without killing the human host too.

Incentives and initiatives

Despite dramatic use of the word 'apocalypse' in our title, it's not quite the end of the world yet. We're certainly in a lamentable position, but many believe the tide is starting to turn as governments and other organizations wake up to the problem and begin to take action to make discovery and commercialization easier for the pharma industry.

In the US, the FDA introduced its Generating Antibiotic Incentives Now (GAIN) program in 2012 to encourage more companies to pursue antibiotic development. GAIN grants qualifying new antibiotics (those that target specific pathogens as listed by the FDA) fast track and priority review status, as well as an extra 5 years of exclusivity. A number of new antibiotics have already benefitted from this program; three of which launched this year for acute bacterial skin and skin structure infections. As part of the program, FDA has also established an Antibacterial Drug Development

The Battle Against Bacteria

Helen Boucher, a member of the Infectious Diseases Society of America (IDSA), gives her latest battle report from the war on drug resistance.

How bad is the situation?

We're right on the edge of going back to an era when we didn't have antibiotics. If that happens, we won't be able to do the things that our patients take for granted: taking care of premature infants, performing transplant surgery, open-heart surgery, and administering chemotherapy… the list goes on and on.

What about positive developments?

We've seen two positive things. The first is that three new drugs have been approved this year. The fact that companies felt there was a regulatory path forward allowed them to develop these drugs. The concern is that we still haven't seen the drugs our patients most desperately need, such as those for Gram-negative infections, so we're hoping that some of the newer initiatives that have come along will help in that regard. The other positive development relates to some of the legislative efforts.

Does more need to be done?

Despite the GAIN act, we're still hearing from drug development companies that scientific, economic and regulatory barriers are still a huge problem. At IDSA, we have been advocating for further incentives and measures to stimulate development of antibiotics. In terms of legislation, the ADAPT (Antibiotic Development to Address Patient Treatment) act would help remove some of the regulatory barriers. In addition, IDSA supports economic incentives for drug development. We've done a lot of work on tax credits and we're also advocating for reimbursement reform so that antibiotics can be valued. This is an area that's really gained momentum. The DISARM act, which will allow for a different kind of payment for antibiotics, provides another legislative incentive.

We're also very focused on investing in diagnostic tests to make sure that we use the antibiotics we do have as appropriately as possible. If we can better ascertain what infection a patient has, we can ensure the use of the best treatment.

How can we facilitate the development of antibiotics?

Public–private partnerships provide an important role in stimulating antibiotic discovery and development. The Innovative Medicines Initiative (IMI) and the New Drugs for Bad Bugs initiative is a public–private partnership that appears to be incredibly effective; some of the things we've seen out of the IMI are revolutionary in terms of collaboration and in allowing the key stakeholders to work together to address the problem. It's not just about developing new antibiotics either. We need to understand more about what's happening with resistance in a real-time way: where the problem is and what's ahead of us.

Tell us about the IDSA's 10 by 20' initiative…

IDSA's 10 x 20' initiative seeks a global commitment to produce ten new systemically available antibiotics by 2020. We have four new drugs now, which is better than a couple of years ago, but there is a long way to go! Part of what's important about the goal is the 10-year horizon. Our message in all our advocacy over the past years has been that as well as meeting the needs of today we also need a robust and renewable pipeline of antibiotics for the future.

Task Force, which includes in its goals the ongoing evaluation of existing FDA guidance for antibiotics and the exploration of new scientific approaches to facilitate drug development in the area.

US legislators have recently been working on the DISARM (Developing an Innovative Strategy for Antimicrobial Resistance) Act. Where GAIN focuses on creating a fast-track FDA review process, DISARM aims to address four core actions that were identified in a November 2013 report from the US Centers for Disease Control: (i) preventing infections and the spread of resistant bacteria, (ii) better tracking of resistance and antibiotic use, (iii) improved use of antibiotics, and (iv) the development of new antibiotics to treat resistant infections. DISARM will also try to overcome some of the financial disincentives for companies by making reimbursement rules more favorable. For example, the US federal healthcare program Medicare currently only reimburses inexpensive, commonly used antibiotics rather than the latest innovations.

As noted earlier, European regulators have been discussing drug resistance seriously since 1998. Indeed, the European Commission took an early lead by developing the European Community Strategy Against Antimicrobial Resistance.

In 2009, an EU–US summit took place, resulting in the formation of the Transatlantic Task Force on Antimicrobial Resistance. The task force aims to increase levels of communication, coordination and cooperation for human and veterinary antimicrobials. Activities include regular meetings and teleconferences between the EMA and the FDA to discuss recommendations on clinical trial designs for new antibacterial drugs, feasible approaches to facilitate trials, and regulatory options available to medicine developers.

Other practical efforts have followed in recent years. In March 2012, Europe's Innovative Medicines Initiative (IMI), a public–private partnership, launched the New Drugs for Bad Bugs program, which offers funding to help support promising projects in the field. Three projects are currently underway: COMBACTE (Combatting Bacterial Resistance in Europe), TRANSLOCATION, and ENABLE (European Gram-negative Antibacterial Engine). COMBACTE is a public–private partnership that will mainly be devoted to performing clinical trials of new antibiotics through a network of experienced investigators, as well as designing and supporting tests to support diagnosis. TRANSLOCATION will focus on increasing understanding of how to get antibiotics into multi-resistant Gram-negative bacteria by studying the molecular basis of cell wall permeability. ENABLE will focus on developing antimicrobial candidates against Gram-negative bacteria for testing.

"As of June 2014, there were at least 43 antibiotics in development, seven of which were in Phase III clinical trials."

At the end of 2013, the EMA also organized an event with the European Commission to look at the regulatory options for approving antibiotics and how to make the most of the current armamentarium. Around the same time, the agency released an addendum to its guideline on the evaluation of medicinal products indicated for the treatment of bacterial infections, which outlines new approaches to development, in addition to giving guidance on data-gathering strategies to facilitate the marketing authorization process (3).

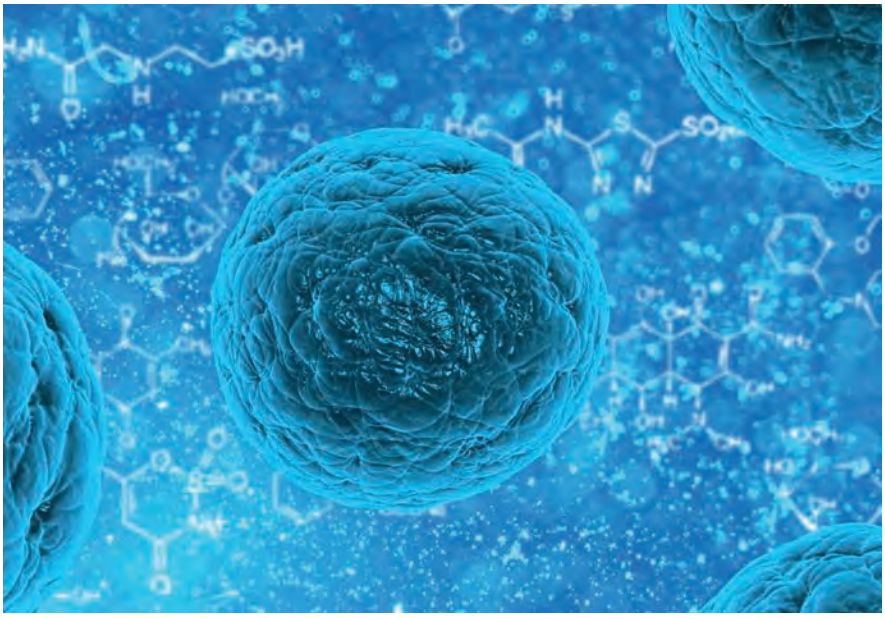
Worth noting is an interesting development in the UK – a new £10 million (around $16 million) award called the Longitude Prize. The prize was set up by the UK government as a grand innovation challenge to solve what the UK Prime Minister described as the biggest problem of our time. Antimicrobial resistance was selected as the subject of the challenge in a public vote. The full details have not yet been announced but entries will be open shortly. The aim is not to develop a new antibiotic, but rather to create a point-of-care diagnostic that helps clinicians to distinguish between viral and bacterial infections quickly, and make better decisions about which antibiotic (if any) to prescribe. It will likely be impossible to completely eliminate antibiotic resistance because of the speed at which microbes evolve, but reducing misdiagnosis and overprescription would at least make some impact.

Now, the pharmaceutical industry must make the most of the initiatives that have been put in place. As of June 2014, there were at least 43 antibiotics in development, seven of which were in Phase III clinical trials (4). In Antibiotic Apocalypse: Part II next month, we take a closer look at the next generation of antibiotics, with input from GSK and Roche.

References

1. *WHO, "Antimicrobial Resistance: Global Report on Surveillance 2014, "April 2014, www.who.int*
2. *Eurosurveillance, "National Policies for Preventing Antimicrobial resistance – The Situation in 17 European Countries in Late 2000", January 2001, www.eurosurveillance.org*
3. *EMA, "New EMA Guidance on Development of Antibacterials to Help in the Fight Against Multidrug-Resistant Pathogens", November 2013, www.ema.europa.eu*
4. *The Pew Charitable Trusts, "Antibiotics Currently in Clinical Development", June 2014, www.pewtrusts.org*

Pushing Stem Cells from Promise to Product



Manufacturing stem cells for use in research is one thing; doing it on a commercial scale – with all the associated costs and scale-up issues – is an entirely different ballgame. Here, I look at the challenges ahead and the groups rising to meet them.

By Neil Littman

More and more stem cell therapies are entering clinical trials. The California Institute for Regenerative Medicine (CIRM) alone has over 90 development-stage programs and expects to have 10 investigational new drug (IND) applications filed by the end of 2014. As companies ponder how to safely deliver these therapies to patients in the most timely and cost-effective manner, process development and manufacturing challenges have been pushed firmly into the spotlight.

Cell manufacturing processes must comply with the current good manufacturing practice (cGMP) and chemistry, manufacturing and controls (CMC) standards of regulatory agencies to ensure that they are made in a safe and reproducible manner. It does not, however, imply that the process is sufficiently robust, scalable, and cost effective to achieve commercial viability. The key to developing sustainable and affordable stem cell therapies lies in allocating capital appropriately across clinical development, process development, manufacturing, and, importantly, in demonstrating safety and efficacy in the clinic.

Regenerative medicine holds huge potential because of its ability to address not just the symptoms but also the underlying causes of disease. Indeed, you would be hard pressed to find another area within medical research that has captured the imagination and hopes of so many people. And that's not surprising when you consider that research is underway to tackle a large variety of therapeutic areas and disease, such as Parkinson's disease, spinal cord injury, heart attack, blood disorders and cancer, to name just a few.

Developing an effective stem cell therapy is only the beginning. It is vital that we consider the practicalities of regenerative medicine; there are many challenges that stem cell therapies need to overcome in order to become a viable and successful commercial product. What if a stem cell therapy was developed that could treat a condition affecting millions, such as diabetes? How would we go about producing, storing and transporting that volume of cells? If we want to see stem cell therapies move into the clinic, it is vital that manufacturing know-how does not lag behind research and development (R&D).

The product is the process

The manufacturing process for a cell product is directly linked to its safety and efficacy, so knowledge of the process is key to developing a fully characterized and understood product. For this reason, a seamless connection between R&D and manufacturing is essential – much more so than in small molecule or even biologics manufacturing. As any change to the manufacturing process can affect the cell product, scale up and cost-effectiveness should be considered early during clinical development. The most expensive part of manufacturing is usually working out the problematic elements that need to be removed or modified as the technology is scaled up. Spotting these early on will save you time and resources.

Ideally, companies need to start thinking about these issues from the earliest preclinical work. Many cell lines being used by biotech companies to generate cell therapy products were originally derived for research purposes – they may lack proper cGMP compliance or donor eligibility (medical histories and consent). At a minimum, these cell lines will require extensive testing before regulators will

Stem Cell Trials to Watch

Type I Diabetes (ViaCyte)
San Diego-based biotech company ViaCyte recently initiated a combined Phase I/II clinical trial of their VC-01 cell therapy. ViaCyte use embryonic stem cells to create pancreatic progenitor cells. The cells are encapsulated in a semi-permeable device, which lets nutrients in, but stops the cells being attacked by the patient's immune system. Safe inside the device, which sits just below the skin, the progenitor cells mature into insulin-producing cells, potentially eliminating the need for daily insulin injections. The treatment could provide what the company calls a "virtual cure for Type 1 diabetes".

Ischemic stroke (ReNeuron)
ReNeuron's treatment involves injection of neural stem cells, ReN001, into the brains of patients left disabled by ischemic stroke. The Phase I PISCES trial, the first clinical stem cell trial in the UK, showed no significant adverse effects, and the company reported "sustained reductions in neurological impairment and spasticity" in the eleven patients treated. Now, a larger Phase II trial is underway, recruiting 41 patients from ten UK centers. Patients in the Phase I trial were treated over six months after their stroke, whereas these patients will be treated 8-12 weeks post- stroke – the company hope that faster treatment will enhance efficacy.

Age-related macular degeneration (London Project to Cure Blindness)
There is a great deal of focus on ophthalmologic applications for stem cell therapies – the eye is immune privileged, easy to access, and even a small improvement in function could have a huge impact on the patient's life. A therapy developed by researchers at a number of UK institutions, in collaboration with Pfizer, to treat age-related macular degeneration (AMD) will begin clinical trials soon. AMD is caused by damage to the cells supporting the retina. The project will generate replacement cells from human embryonic stem cells and transplant them underneath the retina.

allow their use in clinical trials. Another problem that can crop up when moving from animal to human studies is the use of cell medium containing animal-derived products, such as fetal bovine serum. This is common practice in research labs, but in a clinical setting carries the risk of lot-to-lot variability and even transmission of zoonotic diseases. Again, potentially costly and time-consuming bridging studies will be required to ensure that changes in the manufacturing process do not alter the final product. If a process is deemed efficient and scalable early on, these studies will not be required, saving both time and money down the road.

A thorough knowledge of the process, and therefore the product, will lead to a better characterized product that can be finely tuned and adjusted as needed. Developing potency and validation assays is critical in understanding the final cell product. Again, seamless integration of R&D and manufacture is crucial. For example, research on mechanisms of action during the preclinical phase should help identify potential potency assays, which can be refined and perfected throughout the development process and qualified in early-stage clinical trials. A clear measure of the therapeutic potency allows estimates to be made of the volume of cells you will need to manufacture – and allows you to design your process with scale up in mind.

For example, a few skilled lab technicians working in a clean room with adherent cell culture (T flasks) may be adequate to generate cells for tens or even hundreds of patients in a clinical trial – but what happens when we want to treat many thousands? It is unlikely that increasing the number of cleanrooms will be a viable option – apart from the cost, the area needed for adherent culture would quickly cover footballs fields and, regardless of standard operating procedures, slight differences between technicians could lead to unacceptable lot-to-lot variability.

Understanding the critical unit processes in the manufacture of cell therapies in a stepwise manner allows the process to be reduced to a set of steps with well-defined characteristics that can be reproduced at a large scale – the ultimate goal. However, this is all easier said than done!

A helping hand
The good news is that help is available. In the UK, for example, there is the Cell Therapy Catapult, which was established in 2012 to boost innovation and to help to build a leading stem cell therapy industry in the country. The organization maintains laboratories and staff to help companies – both in the UK and worldwide – to improve, standardize, and scale up their cell manufacturing processes. The overall aim is to make cell therapies more financially viable and to 'de-risk' the technology to make it more attractive to potential collaborators. To address Phase III and commercial manufacturing requirements, the Cell Therapy Catapult will manage a new UK Cell Therapy Manufacturing Center, which is receiving $93 million in funding from the UK government, in addition to the existing $116 million of government funding already awarded.

"There are many challenges that stem cell therapies need to overcome in order to become a viable and successful commercial product."

Various organizations are also attempting to help the industry by establishing standards and best practices for the development of cell therapies. For example, the Alliance for Regenerative Medicine (ARM) is aiming to create a public/private collaboration with partners such as the National Institute for Standards and Technology (NIST), the International Society for Stem Cell Research (ISSCR), the International Society for Cell Therapy (ISCT), and others for the benefit of the cell therapy industry as a whole.

In the US, CIRM is dedicated to accelerating the delivery of stem cell therapies to patients, but one of our challenges is in ensuring that we strike the right balance between early-stage manufacturing and process development challenges while driving product candidates towards clinical proof-of-concept. Any avenue that helps therapies achieve faster clinical success – and that means sustainable and affordable cell therapies for patients – is most welcome.

As the technology in the nascent field of cell therapy and regenerative medicine matures and more products enter late stage clinical development, advances in manufacturing and process development will be essential for timely and cost efficient delivery. An analogy can be drawn to the manufacture of monoclonal antibodies, which were first introduced in 1986. Initially, the industry was plagued by low titers and high production costs, but as the market demand grew, companies increasingly poured resources into large-scale manufacturing and process development. The result was the creation of more robust processes that yielded higher expression levels and cell densities, dramatically reducing the costs of production. In my view, this is where the field of cell therapy must ultimately head.

Opportunities for New Technology

A recent CIRM-sponsored roundtable identified eight key manufacturing-related areas to speed up commercialization of stem cells:

- Expanding pluripotent and differentiated cells to large numbers (> 10^{12}) in suspension culture.
- Making culture conditions more hospitable to cells through research on the biology of the cell microenvironment, including 'smarter' bioreactors with better in-process control and feedback loops.
- Methods for enclosed volume reduction without centrifugation.
- Improving yield during cell isolation.
- Small molecules to replace growth factors and cytokines.
- Synthetic matrices to replace biological ones.
- Methods to provide cells in final formulation media.
- Better control over the purity and identity of the product, and increased understanding of the effects of variation.

For further information, see www.cirm.ca.gov.

Neil Littman is Business Development Officer at the California Institute for Regenerative Medicine, San Francisco Bay Area, CA, USA.

Mix with the world of pharma, products, people and solutions

Join the world's leading pharmaceutical event

7-9 October 2014

Paris Norde Villepinte • France

> **"We had plenty of opportunity to make new contacts. We've made an excellent start in terms of beginning conversations with new partners about potential agreements, and we're now looking at several new products."**
>
> **Evi Economou**
> Regulatory & Pharmacovigilance Affairs Manager, Ariti S.A.

CPhI Worldwide hosts over 34,000 visiting pharma professionals, 2,200 exhibitors from 140 countries and more than 100 free industry seminars, covering every pharmaceutical sector under one roof. Attending CPhI Worldwide is the most cost effective way to establish new business relationships, meet with global partners and stay updated on the latest industry trends.

APIs | Generic APIs | Custom Manufacturing | Fine Chemicals | Intermediates | Finished Dosage | Excipients/ Formulation | Biopharma | Ingredients

CPhI worldwide

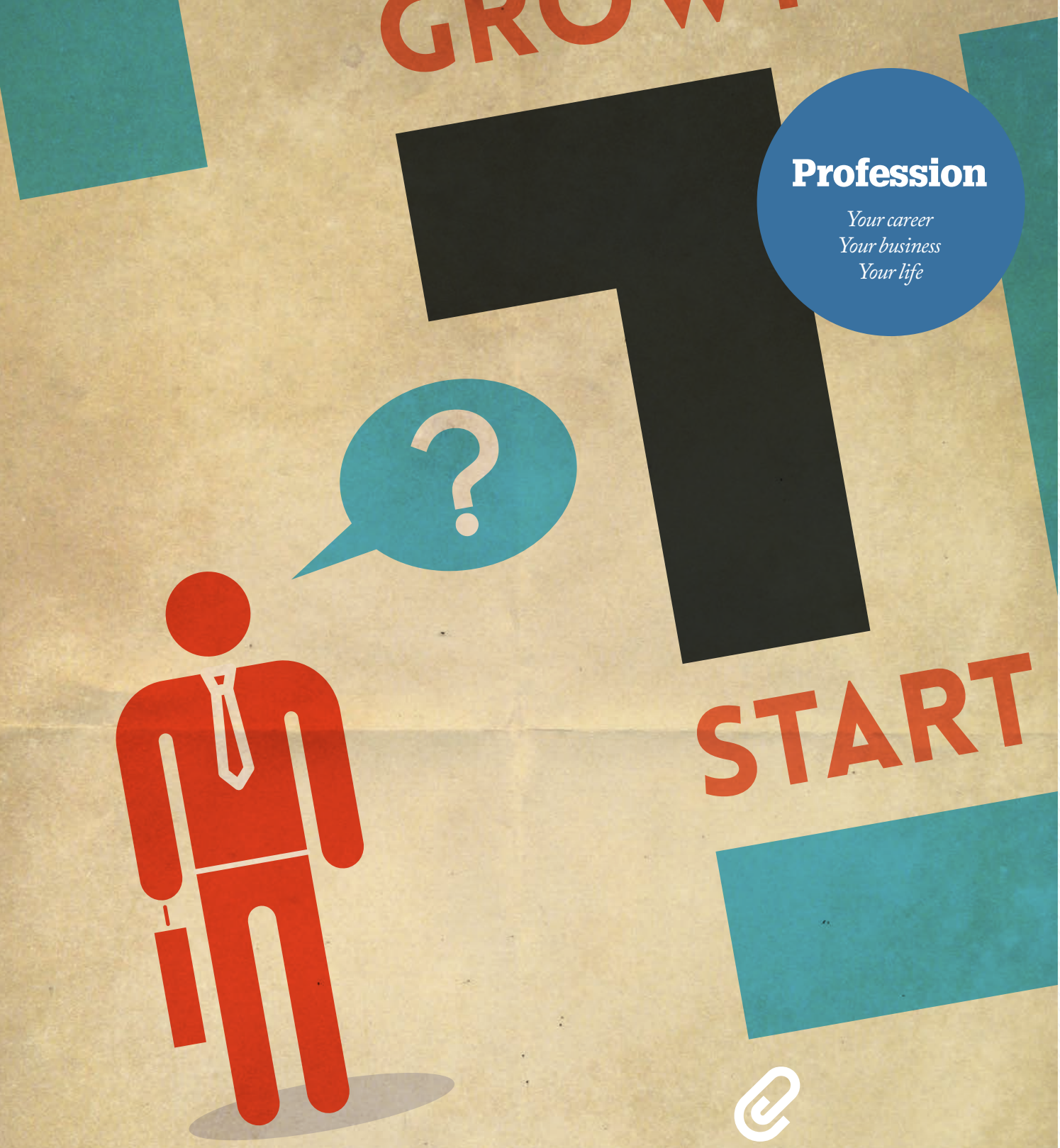
Co-located with

ICSE | P-mec | InnoPack | 25 years Mixing the Global Pharma Community

Register today for free
Use media code: NDWW2016

www.cphi.com/register #cphiww

Organised By: UBM



Tackling Serious Organizational Failure

An FDA Warning Letter can be a real wake up call. How can you address the root of the problem to protect against future violations?

By Peter Calcott

Picture this: you are the CEO of a pharmaceutical company and a Warning Letter from the US Food and Drug Administration (FDA) lands on your desk. The letter informs you that your staff have been caught faking data and recommends that you enlist a consultant specialized in evaluating and rooting out fraudulent practices. Of course, you would be shocked; after all, such an accusation attacks the very nature of what we do and the values we hold dear to our heart. But it goes deeper than that. Don't forget all the patients who were prescribed drugs manufactured by your company. They are likely to be wondering whether the batches they are taking right now are suspect. Even if they examine the drugs, there is no way that a customer can tell if they are good or bad. Trust in both the company and the pharmaceutical in question is lost almost instantly. And it won't be won back quickly or easily, if at all.

If you think this sounds like an unlikely story, you may be surprised to learn that several companies have already received such Warning Letters in 2014 (1-3).

Cutting corners

As a CEO or senior executive, your first instinct may be to assume that it's an isolated incident. But I assure you that it is not; it is endemic in your organization. What could have caused this? The answer is simple: when the drive for volume outweighs the drive for quality, people cut corners to meet the quotas.

After the Warning Letters were issued in the real world examples noted above, the usual posts on LinkedIn followed to broadcast the news. People asked questions and expressed their opinions. After reading several posts, I was perplexed. It seemed that many of the posts focused on 'advertising' their services or posting links to websites listing best practices. But in my experience, all the best practices, standard operating procedures (SOPs), policies and tools in the world are not going to solve this problem. At best they will mask the issues and delay the actual remediation.

"The turnaround to a quality-minded culture cannot be made by rewriting policies and SOPs. It also cannot be made by inspiring speeches at all-hands meetings or emails to staff."

If the management in these companies is serious about solving the problem, they must wake up and engage with their operations to find the root cause. Unfortunately, the answer is often staring at them in the mirror every morning. The management is the problem. They have lost sight of their goal. They have created an environment where the drive is to increase revenue at any cost. They have altered the company culture, intentionally or unintentionally, losing sight of the customer – the patient.

Rescuing quality

The turnaround to a quality-minded culture cannot be made by rewriting policies and SOPs. It also cannot be made by inspiring speeches at all-hands meetings or emails to staff. Culture change can only come when the workers see the CEO and his staff demonstrating the correct behavior. He or she must not only clearly describe his or her new position and expectation to the staff, but be seen to actually do it.

A turnaround of a company in such dire straits can only come from the top. It takes a brave CEO and senior staff to recognize the problem, fix it and be seen to fix it. As a consultant, I am often asked to help facilitate improvements in an organization's quality, manufacturing and process development. One of the first things I do is request an interview with the CEO or President (assuming it is not he or she who requested the change), to determine whether those at the top are on board with the change. It is only after I am convinced that the CEO is sincere that I consider taking on the project. And believe me, I have seen my fair share of non-starters. As a consultant, I believe my role is not to rack up billable hours, but to solve problems.

The CEOs I have interviewed under these circumstances fall into three classes. First, there are the ones who 'get it' (sometimes they only get it after a severe Warning Letter or worse, sometimes it is just a near miss that has shaken them) – these are the ones I will take on. Second, there are those who simply don't get it, often returning to the same mindset: "This is going to cost a lot". Unfortunately, the cost of not making a change is usually much higher and more traumatic. I avoid such CEOs like the plague. The third category is a more difficult beast. They talk about culture change and doing the right thing, but their enthusiasm quickly wanes once they realize they may have to slow down production or set low volumetric goals initially. These ones I try to avoid, if I can spot them early enough.

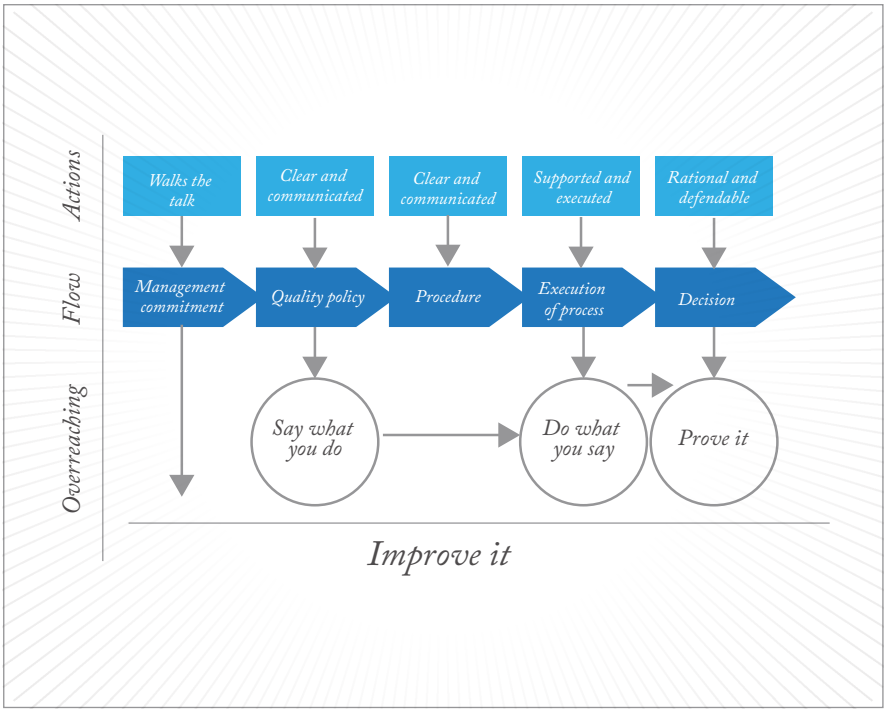


Figure 1. The linkage between management and actions on the "shop floor".

The successful culture shift

So, how do you go about a culture shift? First, you need to maintain momentum; I use the graphic shown in Figure 1, which allows the organization to see where it is going. The philosophy is based on the adage: "Say what you do, do what you say, prove it, and improve it," which covers the important elements of documents, execution and records, with a good dose of continuous improvement. It also places the role of management very clearly front and center in the organization.

As an ice-breaker, I begin the process by giving an overview on a topic of interest to all, such as quality risk management, ICH Q10, or quality by design, to a broad-based group, including quality assurance, manufacturing, quality control, engineering, validation, procurement and logistics. I introduce the program using the graphic in Figure 1 and indicate that we are going to start with a gap analysis. I point out that it is not an audit; there will be no paperwork and corrective action and preventive action (CAPA) reports to manage. I also describe what the culture needs to be like at the end of the project. The sidebar illustrates some of the elements that make up the ideal company culture. With the elements clearly defined,

Top 10 traits of a high performing organisation

1. There is a blame-free culture: we are out to solve problems not punish people.
2. Mistakes are a learning experience.
3. Silos are eliminated.
4. Quality is value added.
5. Quality is a facilitator, partnered with to solve problems.
6. User-centric systems, processes & documents rule.
7. Team-based approaches are encouraged.
8. Human error is manifestation of a broken system, not a root cause
9. Simplicity rules, complexity is driven out.
10. Our QMS is a set of tools to help us accomplish our goals.

"I always look for some quick wins that can be done inexpensively and with little disruption, alongside longer-term goals."

everyone can recognize change as the project progresses.

I interview all the process owners of the quality management system and stakeholders. Basically, I ask them to describe it to me – what do they like, what don't they like, and what are their frustrations. Otherwise known as The Good, the Bad and the Ugly, after that great spaghetti western! It is important that this discussion is open and honest. All discussions are kept anonymous and identities are not reported to management. The goal is to identify what can be improved, not to identify those who can be blamed. I also look for signs in areas where the desired traits are already evident and take an inventory of which elements are either missing or targets for improvement.

By the time I have conducted these interviews, it is surprising how much I have learnt. Here are some common themes:

1. While the organization as a whole engages in 'silo thinking', there are usually little pockets where collaboration is evident across functions. We must now develop ways to propagate this across the organization.
2. People are relieved that somebody has shown interest in what is not working and that somebody is listening.
3. The critiques from the process owners and stakeholders are often identical: everybody knows what does not work. Now that is out, we can work on the solutions.
4. In the gap analysis, everybody feels free to articulate. They take the risk to trust. Of course, some are more open to discussion than others. In the early interviews, I learn and in the later ones I often confirm what I have already heard.
5. A lot of people have very good ideas on how to solve the issues. Taking these ideas, vetting them, organizing and prioritizing is the easy part. The next step is to form the teams that will work on the solutions, focusing on a collaboration, the elimination of silos, and user-centric design.

Building on success

With the analysis complete and project plans outlined, we get management support to embark on a variety of improvement projects. Some problems are expensive and time-consuming to remedy, while others can be done quite quickly. I always look for some quick wins that can be done inexpensively and with little disruption, alongside longer-term goals. These early successes create momentum in the company.

Let me share a short example of success. One company's implementation of a CAPA tracking system had not been executed well; the new software was painful to operate and consequently avoided by many in the workplace. In fact, it was not a software problem but rather a configuration issue. A small project with a broad-based team was empowered to create a solution. The configuration was re-engineered, tested and evaluated by a variety of users, then revalidated. An 'advertising' campaign followed to describe what had been changed, why it had been changed, and what the impact would be. When the newly configured system was rolled out, people started to clamor to use it. The system was no longer a burden – it was a usable tool set that aided the workflow. Seeing the real impact of the success, the organization was inspired to create improvements in other systems. Staff were energized. The culture shift had begun.

Peter Calcott is President of Calcott Consulting LLC, CA, USA.

References

1. *FDA Warning Letter, USV Limited, WL 320-14-03, February 6, 2014.*
2. *FDA Warning Letter, Canton Labs Private Limited, WL 320-14-0, February 27, 2014.*
3. *FDA Warning Letter, Smruthi Organics Ltd, WL 320-14-005, March 6, 2014.*

25 years
CPhI

Come celebrate with us...

We'd like to thank you for supporting CPhI and helping to shape pharmaceutical industry as we know it today…

Network with clients, colleagues and industry professionals, while enjoying a night of cocktails, passed hors d'ouvres and entertainment in the luxurious InterContinental Paris Le Grand, overlooking the world famous Paris Opera.



Wednesday, October 8

8:00pm - 10:00pm
Networking, hors d'oeuvres and open bar

10:00pm
Celebratory speech and anniversary toast

10:30pm - Midnight
Entertainment and dancing

The CPhI Worldwide 25th Anniversary networking party provides an exclusive networking opportunity, and includes a full open bar, drinks and entertainment for the entire night in downtown Paris. Don't miss the chance to celebrate and connect with top industry professionals from around the world!

Tickets can be purchased in the online show registration form. If you have already registered, you can log in with your registration information to purchase tickets.

Limited availability, first come first served bases: € 125

VIP Tables and group tickets
can be purchased by emailing: Chris.Maxwell@ubm.com
For other inquiries regarding the 25th Anniversary Party, please email: cphi@ubm.com

Only 400 tickets available, so order now! www.cphi.com/25

UBM

Boosting Access to Medicine

Sitting Down With…
Wim Leereveld, founder and CEO of the Access to Medicine Foundation

Photo credit: Patricia Wolf.

Where did the idea of the Access to Medicine Index come from?

I had been working with clients in the pharmaceutical industry for over 15 years, leading a successful marketing business. I knew I wanted to do something different; I wanted to improve society. A report from Oxfam came into my hands – "Beyond Philanthropy" – challenging the pharmaceutical industry to do something about the fact that two billion people in the developing world have no access to medicine.

Having worked with pharma, I knew the industry was willing to improve, but they didn't know how. I also knew that, like most companies, pharma companies spend a lot of time looking at their competitors. Of course, they are interested in what governments say about them, they are interested in what NGOs say about them, but mostly they are interested in each other. This is the principle behind the Index. Before the Index, companies were not transparent – and they did not receive recognition for good practice. Perhaps more importantly, they didn't know what their peers were doing to improve access.

So, you had a clear goal – how did you go about making it happen?

Well, it wasn't easy at first. If you ask Oxfam what they think Big Pharma should be doing, you get a different answer than if you ask WHO or an investor. I realized that unless we could find a common path, companies simply could not satisfy everyone. The first big task was to see if all the stakeholders could agree on what they wanted from pharma companies. The second task was to start measuring it; Access to Medicine Index is the result. It's published every two years, and rates the 20 largest pharma companies on their efforts to improve access to medicine in developing countries.

How did people react to the new Index at first?

When I first started talking to pharma companies about the Index, they were not interested. For the first iteration, we compiled the data on each company from public records and sent it to them to check it was accurate. Only eight out of the 20 companies provided feedback. I think they were hoping that, if they didn't react, nothing would happen!

That all changed once the first Index appeared in the UK's "Financial Times". Companies saw that we were giving them truly valuable information. After all, we show what their peers are doing, define what society wants from them and measure how close they are to success. Now, all 20 companies work intensively to provide the requested data for the Index.

Any dark moments?

At the start, there was at least one moment a week when I thought: "What am I doing?" The turning point for me was in 2007 at a conference in New York. The keynote was by Mary Robinson, former President of Ireland and United Nations High Commissioner for Human Rights. During her speech, she announced: "I have been impressed by the Access to Medicine Foundation's efforts to get the stakeholder perspectives of the pharmaceutical companies. I think this is a very important development." I had spoken to her briefly at a reception months before, but I had no idea that she planned to mention the Index! To be recognized by such a respected world leader – I will never forget that moment. I knew then that I would never give up. Or rather, I went from thinking I should give up once a week, to only once every two months!

How is industry progressing along the access to medicine journey?

It takes time. These companies are like oil tankers; an oil tanker can change direction, but only a few degrees at a time. We must be patient. I am convinced that companies are making positive long-term decisions. I speak to CEOs and they know all about the Index and what the company is doing to improve their ranking.

Companies have evolved, and so has the Index. As time goes on we have a more concrete, detailed picture of companies. With every Index we raise the bar. For example, for 2014 we are adding data from South America, so there is a whole new territory to consider. The nature of the Index is that if one company goes up, another must go down. But I am convinced that almost all companies have improved access since we started the Index.

What are your plans for the Index?

Pharmaceutical companies are not solely responsible for access. By only measuring the Big Pharma companies, we are not getting a complete picture. So one of the next challenges is to look at the role of the other main players: generic medicine companies and governments.

How do you feel about what you have accomplished so far?

Starting the Foundation was the best decision of my life. Every day I do something that has never been done before. And it is something that develops our world. It is so rewarding to see practices changing; for example, the development of child dosage forms. I feel I now have the influence to change things for the better. But that doesn't mean my work is finished. I'm on a path and I don't know where it ends.

The 2014 Access to Medicine Index will be published in November.

the Medicine Maker

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

Reason #1: Usefulness

The Medicine Maker will give you:

- The inside track on emerging technologies
- Case studies that troubleshoot real development and manufacturing problems
- Profiles that get inside the minds of the stars in pharma and biopharma
- Best practice and business perspectives from across the industry
- Tips to improve your career and the performance of your team

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

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

Pharma Integrates 2014

Riverbank Park Plaza London

18 & 19 November

Join over 200 senior Pharma executives

London's Premier Pharma Conference

An exceptional networking and learning opportunity

Following the phenomenal and continued success of **Pharma Integrates**, we are delighted to present a formidable speaker line-up of industry leaders at **Pharma Integrates 2014, Riverbank Park Plaza, London, 18 & 19 November.**

- Addressing Pharma's most signifcant strategic challenges
- In excess of 60 senior level speakers
- 240 senior pharmaceutical executives representing all key stakeholder groups attending
- Engaging and interactive panel discussions

David Brennan, Event Chair & Former Chief Executive Officer, AstraZeneca

David will lead a prestigious speaker line-up comprising senior leaders from across the pharmaceutical industry.

Call to Book:
+44 (0)20 8667 9551

For more details see www.lifesciencesindex.com/pharma-integrates

Over 60 speakers including:

Keiran Murphy
President & Chief Executive Officer **GE Healthcare Life Sciences**

Tommy Dolan
Vice President Drug Product and Design, Worldwide Research and Development **Pfizer**

Paula Gildert
Vice President, Global Head of Development Strategic Sourcing **Novartis Pharma**

Clive Badman
Head of Pre-Competitive Collaboration, **GlaxoSmithKline**

Christoph Heinemann
Vice President Strategy & Portfolio Management, **Sanofi**

Wolfgang Renz
Corporate Vice President Business Model & Healthcare Innovation, **Boehringer Ingelheim**

Presented by Life Sciences Index

January 26-29, 2015 | The Mayflower Hotel, Washington, D.C.

CMC STRATEGY FORUM

ADVANCING BIOPHARMACEUTICAL DEVELOPMENT

January 26, 2015

Combination Products for Biopharmaceuticals: Emerging Trends in Development, GMPs and Regulatory Expectations

and

Current Perspectives on Host Cell Protein Analysis and Control: Science, Product Quality and Regulations

WCBP 2015

January 27-29, 2015

19th Symposium

on the Interface of Regulatory and Analytical Sciences for Biotechnology Health Products

Abstract Submission Deadline:
November 26, 2014 for Poster Consideration

Student Poster Submission Due Date:
November 3, 2014 to be considered for a Student Travel Grant

SCAN to browse CASSS for forum updates at casss.org

Organized by CASSS
An International Separation Science Society

CASSS
AN INTERNATIONAL SEPARATION SCIENCE SOCIETY
www.casss.org

best technologies.
broadest expertise.
faster development.

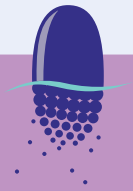
Catalent®

VISIT US ON
Booth 2C9
AT CPhI
IN PARIS

CTLT
LISTED
NYSE

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

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



TECHNOLOGY SPOTLIGHT

RP SCHERER SOFTGEL TECHNOLOGIES

Optimized delivery profile and enhanced bioavailability across versatile liquid or semi-solid formulations, including peptides. Proven partner with over 80% of Rx brands and 200+ Rx products on the market.

DEVELOPMENT DELIVERY SUPPLY

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

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

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