JULY/AUGUST 2016 # 21

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The Innovation Awards 2016

Nominations are open for The Medicine Maker 2016 Innovation Awards and will close on November 16, 2016. The Awards will recognize the most exciting new drug development and manufacturing products released onto the market during 2016.

To be eligible, the product must have been launched (or will be launched) between January 2016 and December 2016. The 'product' can be equipment, software, instruments or technology from any area of drug development and manufacture.

All eligible nominations will be put to a judging panel, who will select the top ten innovations to be highlighted in the December 2016 issue of The Medicine Maker. The overall winner will have the opportunity to share the developmental story behind their product in a 2017 issue of The Medicine Maker.

Nominations can come direct from vendors, or from the end-users of the product.

Nominate now: http://tmm.txp.to/2016/innovationawards
Or email: stephanie.sutton@texerepublishing.com

The Power List 2017

Who are the most influential and inspirational individuals in drug development and manufacturing? This is the driving question behind The Power List. The Medicine Maker's annual Power List, published every April, compiles the top 100 most prominent and inspirational individuals involved in medicine making. Will the members of the 2016 list retain their places?

Nominations for the 2017 list are now open and will close in on February 1, 2017.

The Power List is a celebration of the entire field and process of medicine making, from small molecule to biologic and precision medicines. Anyone who has a part to play is eligible, including academics, technicians, regulators, consultants, vendors, philanthropists – it's up to you to decide who is considered for the list.

The full list of nominations will be passed to an independent panel and the top 100 will be published in the April 2017 issue of The Medicine Maker.

Nominate now: http://tmm.txp.to/2017/powerlist
Or email: james.strachan@texerepublishing.com

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Willis Whitfield stands in an early version of his cleanroom design. Image courtesy of Sandia National Laboratories.

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Turning Failure into Success

In addition to learning from our own mistakes, we should look to Warning Letters – and the subsequent solutions – to benefit from the blunders of others.

As Albert Einstein once said, "The person who never made a mistake never tried anything new." But mistakes in the pharma industry can have serious consequences for patients, which is no doubt one of the reasons the industry can be cautious – it's simply a case of following the inverse of Einstein's wisdom! In reality, not moving with the times can also be an error – outdated facilities or processes can become risk hazards in the eyes of regulators.

Warning letters from the FDA or other agencies are a fact of life in the pharma industry. After all, no facility, process or employee is perfect. Warning letters are publicly available, but the recipients do not like to draw attention to them and remedial action is usually taken quietly. Once uncovered by a journalist in search of a new headline, however, warning letters become very public – and very quickly.

One incident that made headlines in 2015 was a warning letter received by the US National Institutes of Health about its Pharmaceutical Development Section (PDS) and its intravenous admixture unit (IVAU) in Bethesda (1). The letter contained an extensive list of problems.

The subsequent remedial action – the most important part of the ongoing story – was not widely reported, as is often the case. In fact, the NIH pulled together a task force and asked a contract organization for an independent assessment and suggested actions (2). Specific areas of focus included air handling, deficiencies in the facility and equipment, training, standard operating procedures and quality control. The main problem appears to be that the facility was simply out of date; a major rebuild is required to bring it up to speed with cGMP. Ongoing drug production at the PDS has been decommissioned for some time. As for the IVAU, a number of actions have been taken, which were acknowledged by the FDA in a July 2016 letter (3).

Journalists often focus on negativity – perhaps leaning towards the schadenfreude of their readers. But with every industry 'scandal' there are lessons to be learned. By focusing on the solutions to problems – and celebrating innovations that reduce risks or improve processes – we can all move forward; hopefully, with fewer mistakes.

To that end, I'd like to draw your attention to our annual Innovation Awards, which will be published in our December 2016 issue. Nominations are now being accepted at http://tmm.txp.to/2016/innovationawards. And, as proved by our cover feature in this issue, innovation isn't possible without special people – nominations for our 2017 Power List (http://tmm.txp.to/2017/powerlist) are also open. On page 3, you can find more details on both celebratory initiatives.

Stephanie Sutton
Editor

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Upfront

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

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

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Made in China

The world's most populous state is set for big things in patented (bio) pharmaceutical development, according to a new report

China is the second largest healthcare market in the world and is already a significant player in the manufacture of active pharmaceutical ingredients (APIs) and generics. But over the past 30 years, China has independently developed only 40 chemical drugs – most of which have come out of public sector research (1). With a growing middle class population and increased gentrification in China, healthcare standards and spending are increasing, which is leading to greater demand for higher quality drugs and medical technology. Where will this lead in the next 10 years? According to a survey of 71 Chinese and 223 international companies in the pharma industry, China is upping its game and set to develop significantly larger numbers of new drugs in the future (2). Here are some of the main findings from the survey.

China's big pharma

China is a popular player when it comes to exporting excipients and APIs, but 65 percent of international respondents believe that China will be discovering and patenting new chemical and biologic drugs within the next five years.

Chinese firms are expected to discover

drug targets for Chinese populations – and these targets will be researched, trialed and manufactured by Chinese CMOs and distributed by Chinese partners. In other words, China will create its own "American Big Pharma model".

Many Chinese companies are also ambitious about meeting international regulations and exporting their products overseas. In particular, there is huge interest in new biologic drugs. Over 80 percent of foreign respondents predict that China will have the fastest evolving biologics sector over the next decade. Chinese companies are also positive, with 50 percent believing that growth will be faster in biologics and biosimilars than any other pharma supply segment.

In with outsourcing

China's improving manufacturing quality has led to increased outsourcing activity from western companies (including big pharma) to Chinese CMO's and other local manufacturing providers. Fifty-one percent of international respondents believe that commercial manufacturing could be completely undertaken within China, with 35 percent stating they would also outsource packaging to China. However, confidence was low in outsourcing analytical testing to China – only 15 percent of respondents believe that this complex area can be competently outsourced.

Regulation overhaul

Seventy-six percent of respondents stated that their investments or progress in China have been hindered by regional regulatory delays, because of the government's tight control of the pharma market. Seventy-two percent of participants went further, suggesting that a "US-style GDUFA [Generic Drug User Fee Amendments] fee system" is needed, which would deter companies from registering drugs they have no intention of making, thus clearing existing backlogs and speeding up future approvals. Moreover, 94 percent of Chinese companies believe the Chinese FDA needs to quickly grow to a size that is more comparable with US FDA, if it is to properly regulate the Chinese pharma industry. *JS*

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Giving Cancer the Old One-Two

First, zap the tumor with radiation to trigger P-selectin expression. Second, release a targeted attack of drug-loaded nanoparticles

Countless anti-cancer compounds have failed in development because of problems related to specificity. Previous research has suggested nanoparticles as a potential means of delivering anti-cancer drugs directly to the tumor site, but targeting is still difficult because of the vascular barrier surrounding most solid tumors. Now, researchers from the Memorial Sloan Kettering Cancer Center in New York, USA, believe they can target the cancer vascular specifically. How? By zapping cells with radiation to trigger P-selectin expression in tumor blood vessels, and then using fucoidan-based nanoparticles to deliver drugs to the target (1). Daniel Heller, co-author of the paper, tells us more.

Why is it so difficult to combat cancer?

Most cancer drugs have a two-in-one specificity problem: the drugs often don't act specifically on the tumors and don't localize specifically to tumors. Many drug companies are focusing on the first type of specificity – how do we make a drug toxic only to a tumor? One difficulty with this approach is that almost every effective compound has some sort of off-target effect, which often limits the dosage and prevents the drug from substantially affecting the tumor. Our thinking is that if we can't depend on a drug to be specific enough by itself, then we should improve its specificity by targeting it physically to the tumor site.

What is the story behind your research?

We first developed our fucoidan-based nanoparticles to target P-selectin, which is spontaneously expressed in tumor blood vessels (without radiation). We knew that fucoidan binds to P-selectin so we decided to make a nanoparticle for drug delivery out of it. Using fucoidan also avoids the complication of synthesizing a nanoparticle with an antibody bound to it.

After obtaining some interesting results showing that the nanoparticle can target tumors that express P-selectin spontaneously, we started talking to Adriana "Ady" Haimovitz-Friedman, a radiation biologist whose lab happens to be two doors down from ours. Ady knew the work of Dennis Hallahan, who showed that P-selectin can be induced in tumors via low doses of radiotherapy.

We worked with Ady to determine whether this process could help to guide nanoparticles to the tumor site. And the answer was, "yes": introducing nanoparticles shortly after irradiating a tumor with just a single, low dose of radiation can result in strikingly efficient anti-tumor efficacy.

What are the benefits of targeting drugs in this way?

New "targeted" therapeutics and precision medicines, like MEK inhibitors, can be used with our nanoparticles to significantly reduce their side effects. Not only did we show that the nanoparticles allowed for much greater doses of chemotherapeutic drugs to be delivered to the tumor site, but we also showed (in collaboration with José Baselga's lab) that the pharmacokinetics, pharmacodynamics, toxicity, and efficacy of a drug can be drastically improved by physically targeting the drugs to the tumor. For example, tumor-targeted nanoparticles can localize MEK inhibitor in the tumor site, resulting in prolonged inhibition of pERK (which promotes cancer cell proliferation). MEK inhibitors have been known to cause serious dermatologic side effects, but our work showed that the drug doesn't reach or affect the skin when it is administered using the nanoparticles. This pharmacodynamics approach to studying nanoparticle drugs is a new step in nano-drug development.

Next, we plan to partner with others (including drug companies) to develop new nano-precision therapies based on drugs in need of improvement.

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Tapping into Data Transparency

A website exists to help researchers obtain clinical study data, but how useful is it?

The need for more transparency in clinical research is being increasingly recognized by the pharma industry. Indeed, a number of companies have now committed to sharing patient data from the studies they sponsor. The Clinical Study Data Request (CSDR) website was rolled out to centralize communication between researchers and sponsors. Researchers can use the site to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research, providing access is approved by the Independent Review Panel.

Isabelle Boutron and her colleagues from Paris Descartes University, France, decided to find out how useful this resource is. The team evaluated the completeness of data sharing on CSDR, for all listed drugs (other than vaccines) by all sponsors actively involved in data sharing (defined as having listed at least 100 studies by June 2014) (1).

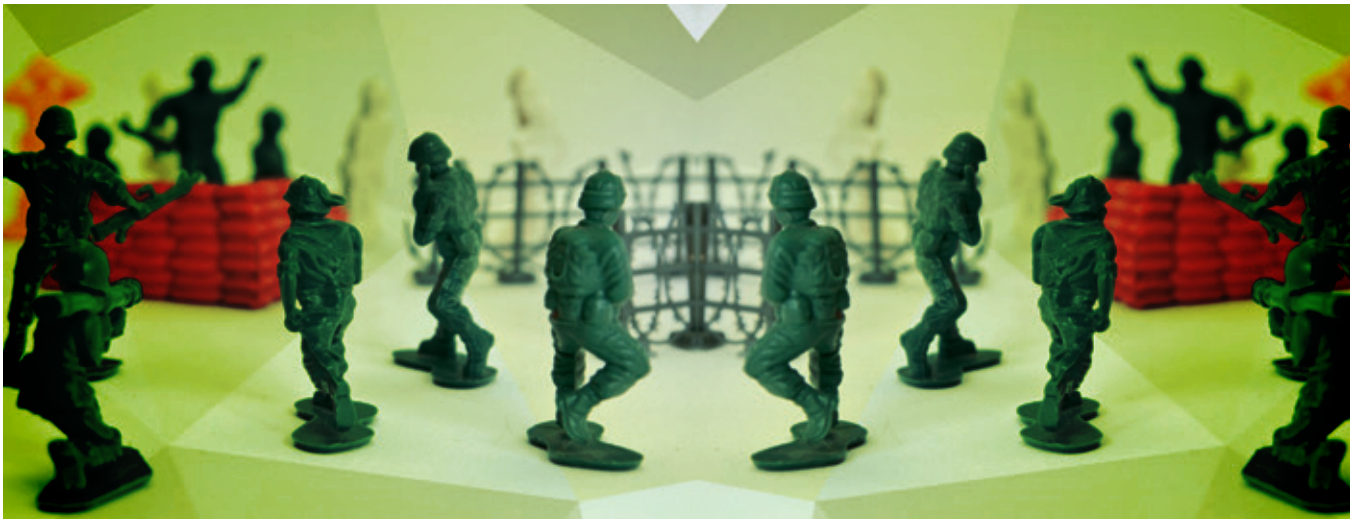
The authors identified 61 drugs (from four sponsors: Roche, 13; Lilly, 3; Boehringer Ingelheim, 5; GlaxoSmithKline, 40), which had been evaluated using 966 randomized clinical trials (462,751 participants) registered at ClinicalTrials.gov. Of these, 53 percent (representing 74 percent of participants) were listed on CSDR, with the percentage varying from 33 percent to 66 percent depending on the sponsor.

Boutron only checked whether registered trials were listed on CSDR, but researchers are also able to submit enquiries to some sponsors to ask about the availability of data from studies that are not listed. "Consequently, our results may underestimate the number of studies for which the data are shared," she admits.

Lack of transparency and data-sharing in clinical research can lead to considerable waste of research. According to Boutron, 30 to 50 percent of trials never publish results and, on average, it takes around two years before results for completed trials are published. That said, the findings do at least demonstrate that sponsors are regularly adding some studies to CDSR. Boutron recognizes that providing access to data takes time and effort. But the process is evolving, and Boutron believes that other stakeholders could be more involved: "The regulators should be doing more to encourage data sharing – and researchers need to work on processes to facilitate data sharing." *JS*

Reference

1. *I Boutron et al., "Sharing of data from industry-funded registered clinical trials", JAMA, 315, 2729-2730 (2016). PMID: 27367768.*



Biopharma Battlefield

Can portable kits manufacture on-demand biopharma medicines for remote soldiers?

Biopharmaceutical medicines remain demanding in terms of manufacture and storage, meaning that they are not readily available in all locations. How do you get much-needed biologics to soldiers fighting in remote locations, for example? A number of research teams are working on that issue, with funding from the US Defense Advanced Research Projects Agency (DARPA). DARPA has proposed that miniaturized synthesis and manufacturing platforms that make medicines on demand could be the answer.

One such platform, developed by scientists at MIT as part of the Bio-MOD (Biologically-derived Medicines on Demand) initiative, uses programmable yeast cells to produce therapeutic proteins (1). The researchers genetically modified the yeast strain Pichia pastoris so that it is able to produce one of two proteins, depending on which chemical trigger the cells are exposed to. When exposed to estrogen β-estradiol, the cells produce recombinant human growth hormone (rHGH), but when exposed to methanol, the cells produce interferon-α2b.

The yeast cells are contained within a table-top microbioreactor that contains a microfluidic chip. The device continuously monitors oxygen levels, temperature and pH to ensure the optimum environment for yeast cell growth. If a different protein is required, the liquid medium is simply flushed through a filter, retaining the yeast cells (unlike other microbioreactors). Fresh medium, containing the new trigger chemical, can then be added to start production of the required protein.

Another project funded by DARPA is the work of Govind Rao, a professor of chemical and biochemical engineering at the University of Maryland, Baltimore County, and his collaborators at Ohio State University, Thermo Fisher Scientific, and Latham Biopharm. Rao has developed a portable briefcase-sized kit that produces FDA-approved biologics on-demand (2). Rao's kit is different in that it does not require live cells and instead relies on Thermo Fisher Scientific's cell-free expression platform to produce biologics in a matter of hours.

According to Rao, Bio-MOD program manager, Colonel Geoffrey Ling, has personally experienced an unreliable medicine supply chain in remote areas of Afghanistan. "Ling decided to challenge the scientific community to come up with a solution to the problem by inventing technology that would produce protein drugs, at the point-of-care, in under 24 hours," he says.

Rao and his team are now working on making the device robust enough to withstand harsh warzone environments. But the battlefield is only one application of the DARPA-funded projects – it could also be used to revolutionize the availability of advanced therapeutics to low-resource countries or, in the hands of researchers, to empower faster discoveries of products for rare diseases. *JS*

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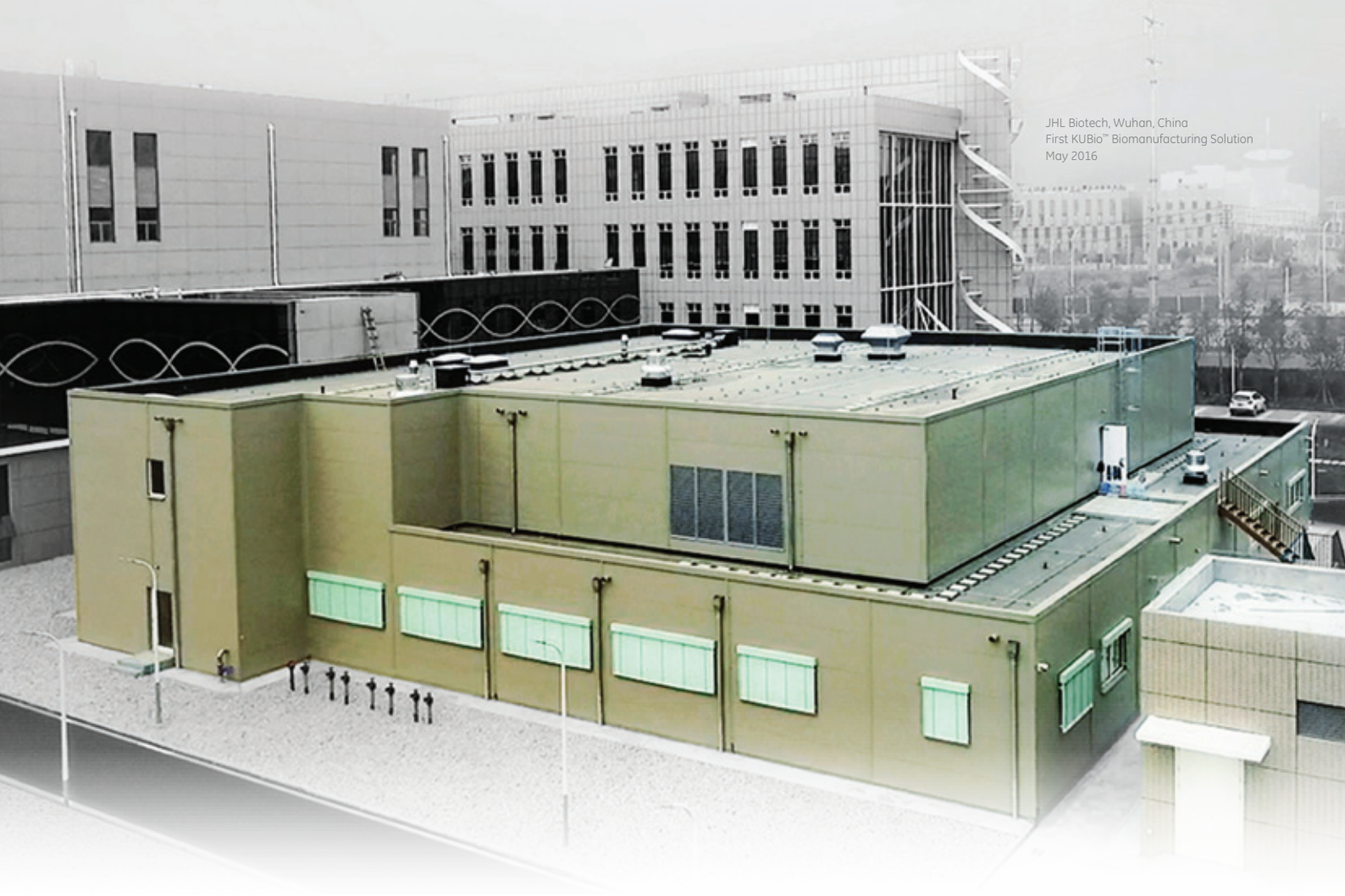

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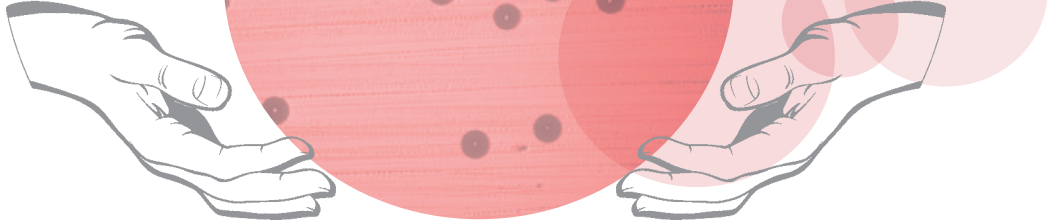


Too Close for Comfort?

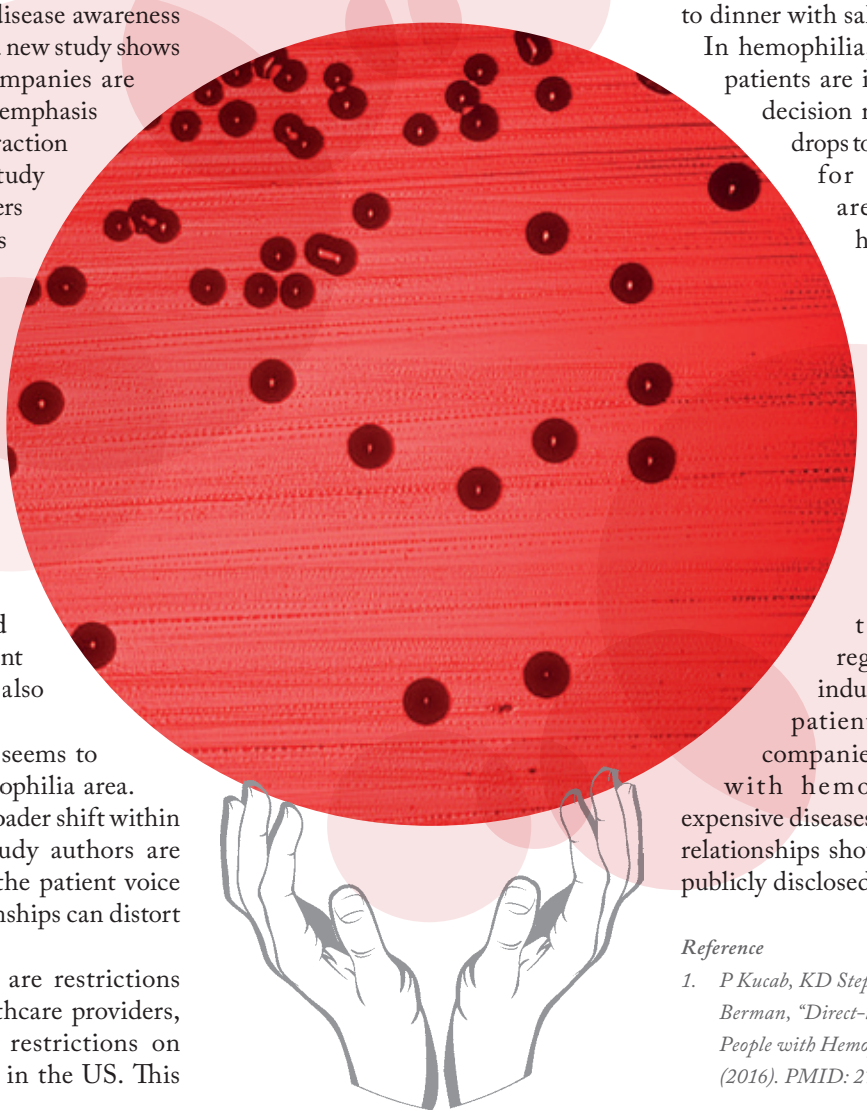
Researchers call for more oversight as some pharma companies cozy up to hemophilia patients

Pharma companies have long targeted their more direct marketing efforts at the physicians who prescribe their drugs, with patients typically being reached only through advertising (where permitted) or disease awareness campaigns. However, a new study shows that some pharma companies are now putting a greater emphasis on direct patient interaction (1). In particular, the study found that manufacturers of hemophilia drugs have recruited hemophilia patients (and their family members) for "employment, consulting roles or advisory boards". Others who are well connected in the hemophilia community, including staff and volunteers from patient advocacy groups, have also been targeted.

For now, the move seems to be limited to the hemophilia area. But could it signal a broader shift within the industry? The study authors are concerned; although the patient voice is crucial, close relationships can distort medical discourse.

"Even where there are restrictions on marketing to healthcare providers, there are almost no restrictions on marketing to patients in the US. This is an unregulated area that needs to be regulated," says Adriane Fugh-Berman, Department of Pharmacology and Physiology, Georgetown University Medical Center, USA. "The same tactics that are used to affect physician choices of therapies are now being used to affect patient choices. Patients should be making healthcare decisions in partnership with healthcare providers who have no conflicts of interest."

According to Fugh-Berman and her co-authors, the industry has begun establishing lifetime relationships with people with hemophilia. For example, Baxter sponsors Camp Superfly, a summer camp for children with hemophilia, to which it sends sales representatives to help staff the camps to "establish personal relationships with young campers". Young adults with hemophilia may also be offered paid internships, college scholarships, awards, career counseling, and insurance counseling. They are also recruited to consumer and professional advisory boards, and offered paid consulting opportunities. In some cases, there have been reports of patients being taken out to dinner with sales representatives.



In hemophilia, about 50 percent of patients are involved in their own decision making, whereas this drops to 5 percent or 20 percent for other therapeutic areas. "Patients with hemophilia are targeted because they control the market share," says Fugh-Berman. "Whoever controls the market share, be it physicians, patients, or payers, will be targeted for marketing."

Fugh-Berman believes that it is time to consider regulatory controls on industry interactions with patients. "Pharmaceutical companies are using patients with hemophilia and other expensive diseases as sales people. These relationships should be regulated, and publicly disclosed and debated." *JS*

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In My View

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

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

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

A Recipe for Brexit Success

Is leaving the EU a foolish or admirable decision? The UK still has a way to go before the shape of Brexit becomes clear, but the pharma industry can succeed if the right policies are put in place.

By George Chressanthis, Principal Scientist, Axtria, USA.

"It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness…" – Charles Dickens, A Tale of Two Cities (1859).

The words of Dickens highlight the internal conflict facing the UK people following the referendum. Like many Americans, I've been intrigued by the UK debate surrounding the Brexit vote. The new Prime Minister, Theresa May, has vowed "to make Brexit a success," so clearly there's no going back. So what must happen going forward to ensure continued success for the UK biopharmaceutical industry? The word "continued" must be emphasized because the UK already has a dynamic pharmaceutical industry. Large global players like GlaxoSmithKline and AstraZeneca are headquartered in the country, with significant research facilities, and numerous other major and smaller biopharmaceutical firms have major operations there too.

And what is "success"? I'm a passionate believer in the philosophy of Roy Vagelos, former CEO of Merck Sharp & Dohme, who believes that a company focus on addressing unmet medical needs by improving patient health through extraordinary science will also benefit shareholder value, while also garnering respect from society for its accomplishments. The lifeblood of any pharma company is its ability to sustain drug innovation through prudent risk-taking, whilst also making effective investments in R&D that mitigate significant uncertainties throughout the entire project/product lifecycle. Thus, if the UK pharmaceutical industry is to continue thriving in the future, political and business leaders will need to develop policies that sustain the environment required for drug innovation and development, post-Brexit vote.

The global pharma industry is on the cusp of tremendous change, as expertly noted by the IMS Institute for Healthcare Informatics, which highlighted the many opportunities, challenges, and uncertainties that lie ahead (1). Given experience and insight gained from my past 34 years as a big pharma executive, pharma industry consultant, and academic economist/public policy/pharma researcher, I'd like to offer some outside-UK policy perspectives on what I think UK leaders must do in a post-Brexit world to sustain the country's pharmaceutical success.

First, continued intellectual property protection is essential for continued R&D and incentives for biopharmaceutical innovation – academic research continually highlights this factor as the most important to sustaining innovation (2). Second, immigration policies must be tailored to ensure the attraction and retention of highly specialized skilled labor to the UK. However, this labor force also needs to encompass the draw of talented graduate students at UK universities, who often work on basic research projects in collaboration with pharmaceutical firms. Not surprisingly, like in the US where

"The global pharma industry is on the cusp of tremendous change."

biopharmaceutical clusters have formed around – and collaborations developed with – major academic centers, we see similar movements in the UK around its premier research universities; for example, AstraZeneca has established a major global R&D center at the Cambridge Biomedical Campus. Third, various forms of capital are also required to work in conjunction with skilled labor for sustained R&D success, such as specialized scientific capital equipment, public infrastructure, and funding of basic research through governmental, research foundation, and venture capital organizations. Prior empirical work has shown that the collaborative US R&D model across the biopharmaceutical research ecosystem (although fragmented) has a greater proportion of riskier projects in their portfolios than their European counterparts (3). This evidence confirms prior work on the importance of economies of scope (not scale) in positively affecting R&D productivity (4). As the pharma industry shifts its R&D emphasis to specialty medicines involving large molecule, biologic, and genomic approaches, a UK environment capable of sustaining a culture of innovative scientific R&D will become even more crucial. Lastly, a UK-EU relationship must not disturb transnational pharmaceutical alliances. Prior empirical work has demonstrated that products developed with alliances have an increased likelihood of success for the more complex phase II and II clinical trials (5).

The UK always seemed to have a "one foot in" approach to the EU; it never adopted the Euro and its geographic separation from mainland Europe has affected its own political and social development. I view the challenges that lie ahead as opportunities for the UK and its pharma industry. As long as wisdom prevails over foolishness, the best of times can still lie ahead.

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There Was Plenty of Room at the Bottom

What began 56 years ago as a vision of miniaturization is now beginning to have a profound influence on drug delivery.

By Merari Tumin Chevalier, Doctoral Fellow, Group Polymer Matrix Composites (CoMP), INTEMA School of Engineering, National University of Mar del Plata, Buenos Aires, Argentina.

In December 1959, Richard Phillips Feynman – theoretical physicist – highlighted the tremendous opportunities offered by miniaturization: "I would like to describe a field, in which little has been done, but in which an enormous amount can be done in principle". Although it was 56 years ago, Feynman recognized the huge potential of small-scale manipulation and control (1). He also offered a challenge, "Why can't we write the entire 24 volumes of the Encyclopedia Britannica on the head of a pin?"

Nowadays, the term "nano" plays a leading role in "the science show", but it's no longer simply a reference to the ancient Greek word for dwarf, νᾶννος (nánnos), or the prefix in the International System of Units indicating one nanometer is one-billionth of a meter. We now use "nano" when talking about how matter behaves at the nanoscale and how that behavior extrapolates to real applications, such as medicine.

After reading the transcript of Feynam's lecture, I fully appreciate why some people call him the father of nanotechnology. He foresaw a colossal sandbox for scientific discoveries at the nanoscale – and within it nanomedicine. The National Institutes

of Health aptly described nanomedicine as "an offshoot of nanotechnology, which refers to highly specific medical interventions at the molecular scale for curing disease or repairing damaged tissues, such as bone, muscle, or nerve" (2).

But can we become "the nanomedicine makers"? I think that we can. Over the years, diseases such as cancer have kept researchers looking for new alternative treatments with improved therapeutic effects and patient welfare. Delivery and release of drug molecules to specific sites represents a big challenge for the pharmaceutical sciences. However, a new frontier in the field of biomedical technologies has opened with the development of novel drug delivery: nanodevices.

Among all the drug delivery nanosystems, I have a predilection for one in particular: biopolymeric nanoparticles. When I talk about nanomedicine, I always remind my audience about how minuscule the world I'm presenting actually is. After all, we are human beings used to living in the macro scale, so it is very useful to exercise our perception of nano objects; consider that a tennis ball is the same size in relation to the Earth as a nanoparticle is to a tennis ball. Why are we so determined to invest our energies developing and obtaining such tiny pharmacological intermediates? Because the effort is worthwhile.

Over this past decade, there has been a remarkable revolution in nanoparticles made from different biopolymers. Such polymeric drug carriers are exceptionally valuable for biomedical applications because of their adaptability to achieve the most critical goals of drug delivery approaches such as:

- carrying a wide variety of active pharmaceutical ingredients (APIs)
- protecting APIs from degradation in the body before reaching the target site
- customizing drug release rates in the specific target site to achieve adequate pharmacological response
- surface chemistry suitable for active targeting, long circulation, and stealth behavior
- delivering the drug intra or extracellularly, depending on the therapeutic goal
- biocompatibility and biodegradability for secure and safe human administration.

I believe that biopolymeric nanoparticle drug delivery systems are extremely valuable; it seems that the best things really do come in small (nano) packages. Something tells me that Richard Feynman wouldn't be surprised with the huge progress that nanopharmacology is achieving – after all, he was the one who imagined small machines working in our bodies. The title of Feynman's presentation in 1959 was "Plenty of Room at the Bottom" and he was right. There is plenty of room at the bottom – perhaps more than we can even dream about.

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Still Sieving...

Isn't it time to move with the times and relegate manual and outdated processes?

By Paul Kippax, Leader – Advanced Materials Group, at Malvern Instruments, Worcester, UK.

"Tried and tested" can be a formula for success, but it's also important to recognize when an analytical technique has drifted into the realm of being tedious and taxing. There are a number of techniques in pharmaceutical production that could fall into this category, but I want to focus on sieving. Sieving has been used to size particles for centuries, but is it fit for the modern pharma manufacturer?

When considering the demands of quality assurance and quality control (QA/QC), queues at the loading bay are unacceptable and costly, so you need a rapid answer to the question, "Can I accept this?" Sieving gets the job done, but there are newer, automated particle sizing techniques available, such as those based on light-scattering measurements.

You may think me biased, but I can say with confidence that laser diffraction is becoming a popular alternative to sieving. I'll admit that the initial outlay is more expensive, but these costs are easily dwarfed by ongoing savings, especially from productivity gains; laser diffraction requires much less manual attention and is also faster. By using laser diffraction, the time to result is cut to under a minute, compared with a minimum of 10 to 15 minutes with sieving. Furthermore, with a typical stack consisting of just five to eight sieves, sieving offers far lower resolution than laser diffraction, which reports around 100 size classes. Poor resolution can result in a failure to detect subtle differences between samples, thereby obstructing the quest for effective and reliable QC. In contrast, our

clients say that laser diffraction pays its way by consistently returning repeatable and reproducible measurements at a speed that eases QA/QC processes.

Resolution is also an important gain when it comes to accelerating formulation development, but here it is the ability of laser diffraction to precisely quantify fines, as well as coarse particles, that is the major benefit. For all pharmaceutical products, from tablets to inhaled formulations, fine particles are important when it comes to controlling dissolution and bioavailability. Controlling fines is crucial from a product quality perspective, and also important when considering processability because excess fines can compromise flow through a tablet press, for example. If you can't accurately measure fines, then how can you learn about their impact on critical quality attributes?

Advances in laser diffraction technology have extended its range to below 100 nm in size, while sieving remains optimally suited to far coarser particles; below 100 µm, sieves become susceptible to clogging as the forces of attraction between particles start to rise. Switching to wet measurement may address this issue, but can also increase the practical burden of measurement. A laser diffraction system, on the other hand, covers the entire particle size range of interest using a single optical set-up.

Moving from manual to automated techniques cuts the training burden and makes it easier to transfer a measurement and associated specification. Today's lab technicians are called upon to apply a growing range of techniques, increasing the risk of operator-to-operator variability creeping in, especially when the analytical process is lengthy. "Deskilling" via automation eliminates this risk and safeguards data integrity. Equally important, a locked-down standard operating procedure (SOP) is readily transferred to a different lab, different geography or to an outsourcing company. A laser diffraction method can accompany a product as it exits the lab and transitions to commercial manufacture, no matter how the manufacturing process is ultimately implemented. Real-time particle sizing, with an in- or on-line system is also an option since it's a proven process analytical technology for automated process control and real-time release.

The pharma industry today is pressured by a number of trends including increased supply chain complexity, concerns over outsourcing, analytical skill shortages and the need for greater manufacturing efficiency. I believe it's time to re-examine the rationale for using manual techniques when newer options are available. Don't you?

KEEP IT CLEAN

Cleanrooms are vital when it comes to ensuring that medicines are contamination free – and yet the technology behind them is well over 50 years old. Is it time for a makeover?

By Stephanie Sutton

Courtesy of Sandia National Laboratories

Cleanrooms are such an important part of pharmaceutical manufacturing that it's difficult to imagine a time when they didn't exist. But surprisingly, cleanrooms are a relatively new invention compared to the history of the pharma industry as a whole. Many of today's pharma giants trace their origins back to small apothecary shops in the late 1800s and larger-scale manufacturing didn't take shape until the 1900s. At this time, there were no true cleanrooms, although efforts were made to minimize contamination by segregating certain areas, which had their own basic filtration and air conditioning systems as technologies began to emerge.

"The first clean room standard (FED 209) was published in the US 1963 and revised in the 1970s, but it was some time before these developments impacted other countries, such as the UK," says John Challenger, chairman at the WH Partnership (WHP), an engineering company based in the UK. "At the time, operating theaters in the UK were relatively crude and included wooden doors and window frames, and plaster walls with virtually no radii at the junctions between walls and floors. Ceilings were often in suspended grid form with simple clipped-in tiles. Unidirectional airflow patterns were not common and invariably filtration was applied in plant rooms rather than at point of entry. Moreover, many old cleanrooms contained high levels of asbestos. In fact, I can recall replacing a large number of cleanrooms in a major vaccines manufacturing facility that had been built in the 1960s – we found white, blue and brown asbestos throughout."

Mr Clean

The father of the modern cleanroom is Willis Whitfield, who worked for Sandia National Laboratories. After considering the dual challenge of unwanted particles and turbulent airflow, Whitfield – dubbed "Mr Clean" by TIME magazine – came up with the laminar-flow cleanroom. Based on a simple design – filtered air is blown in from the ceiling at a steady rate and then sucked out through the floor (gravity assisting with particle removal) – the flow system created a work environment that was more than a 1000 times cleaner than the 'cleanrooms' in use at the time. Admittedly, the competition simply relied on tightly sealed rooms and the use of gloves and garments. Nevertheless, when the first laminar-flow cleanroom was tested, the particle counters registered zero and Whitfield and his colleagues assumed they were broken (1).

The original objective of Whitfield's invention was actually to help with the creation of nuclear weapons during the Cold War rather than to revolutionize healthcare and medicine making. In the 1960s, huge strides were being made in electronics and mechanical components, but microscopic particles can be a serious problem when working with such delicate devices. A physicist by background, Whitfield and his group were asked to come up with a solution to help deal with the nuisance particles. Not long afterwards, Sandia patented the laminar-flow cleanroom, but released it into the public domain so that it could be freely shared. Within just a few years of the breakthrough, $50-billion dollars' worth of cleanrooms were being built worldwide (1). Whitfield passed away at the age of 92, in 2012, and was posthumously inducted into the US National Inventors Hall of Fame.

"Initially, cleanrooms in pharma borrowed a lot from the electronics industry: a simple room, recirculating large quantities of HEPA-filtered and positively pressurized air to adjacent spaces," says Bill Rattray, a pharmaceutical specialist at CRB Consulting Engineers. "Over the years, pharmaceutical cleanrooms have evolved into complex multi-room suites of varying requirements for temperature and humidity control, clean classifications and relative room pressures."

Time for a change?

Given that much of what we understand about cleanrooms and particle control is based on Whitfield's work of over 50 years ago, it can feel like little has changed since then. After all, Whitfield's laminar flow design is still in use across many industries today – and it's still having a huge impact on the electronics industry, where it all began. So has the cleanroom industry been dry of innovation? "Overall, I don't think there have been many advances in air handling systems – and the costs haven't come down that much either," says Tee Noland, CEO of contract services provider Pharma Tech Industries (USA). "When you look at a cleanroom, the lion's share of the complexity and the cost is in the air filtration and handling, which varies depending on how much interchange is needed and the requirements for pressure and humidity. For example, since we work with a lot of powders, humidity is very important for us. And to that end, there have at least been developments in terms of sensors."

Indeed, sensors can be incorporated into HEPA filters to monitor velocity, temperature, humidity and other factors in different parts of the cleanroom facility. Subsequently, there have been advances in data management systems to process sensor information.

But when it comes to adoption of new cleanroom technology in the pharma industry, change can be difficult. "The main reason cleanrooms haven't advanced has a lot to do with operating in a regulated environment. With an FDA-regulated facility, people are inherently resistant to taking risks that are required for change to take place," says Rattray.

"Pharma companies are very cautious about the application of novel or unproven technology," adds Richard Anderson director of WHP. "That said, I do believe that novel clean room techniques are being adopted, where there are compelling reasons to do so. I remember when the handling of a category 3 pathogen needed to take place in a Class 100 (Class A) environment. Now it can take

"FDA regulations remain stringent but have loosened in terms of allowing a more risk-based approach to facility and process design."

place in a safety cabinet or isolator with a negative to atmosphere room with HEPA filtration on the extract."

Very slowly, change is coming. According to Rattray, regulators, like the FDA, are starting to make it easier to adopt new technology. "FDA regulations remain stringent but have loosened in terms of allowing a more risk-based approach to facility and process design. People have realized that in order to make the changes necessary for advancement, we must realistically evaluate these risks through risk analysis."

Investing in advances

"Cleanroom monitoring has always been heavily regulated, but it is possible to be innovative within the available frameworks," says Joe Govier, managing director at Connect 2 Cleanrooms in the UK. "I'm seeing a trend towards increased automation – automated canopies are very popular for us at the moment."

Govier also notes that "smart" advances are also important. For example, the trend of increased trust in mobile and app-based technologies in secure industries, such as banking, has given companies confidence to harness smartphones for other needs. "It's now possible to bring an Internet of Things approach to cleanroom control. Companies can employ advanced monitoring and control across numerous environmental parameters to optimize cleanroom spaces," says Govier.

"Beyond air handling and filtration, there has been a lot of work on the design of the cleanroom and its equipment to help with sterility, but much of this innovation has been driven by regulatory requirements," says Eric Kaneps, a vice president at Pharma Tech Industries. "I also think that the development of isolators and restricted access barrier systems (RABS) have had a big impact on the industry."

Challenger agrees: "The use of isolator technology is one of the key developments in the design of cleanrooms. In particular, the potential for reducing operating costs and significantly improving cleaning and decontamination of critical manufacturing zones is clearly an advantage. Whilst there are some ergonomic disadvantages in the use of isolators, the ability to create a solid barrier between products or hazardous materials and the surrounding environment is a major advantage."

In terms of cleanroom fabrication, the manufacture of clean room panels, flush-glazing systems, clean room components and other architectural features have all helped to improve the ability to maintain operating conditions. "I think that the key advances have been wall and ceiling finishes, wall assemblies and support products. Cleanroom standard accessories are available so that we can use "off-the-shelf" products; we can open catalogues and select cleanroom accessories rather than having to custom build items," says Melissa Holshouser, senior facility planner at CRB. "There is also greater focus on closing processes so that more operations and support functions can be performed in controlled-non-classified production areas."

As well as the main design and structure of the cleanroom, attention needs to be paid to smaller details too. Everything that

Controlling Contamination

- A typical human sheds more than 58 million skin cells per day
- That's around 40 thousand skin cells shed every minute
- Of these, around 10 percent carry microorganisms
- The outer layer of human skin can host up to one million microorganisms per square centimeter

Movement can generate particles in a cleanroom:

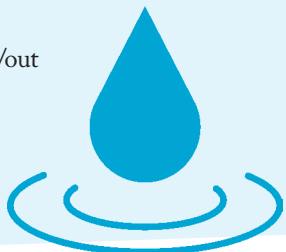
- Sitting without moving = 100,000 particles per minute
- Moving a hand or arm = 500,000 particles per minute
- Standing up or sitting down = 2,500,000 particles per minute
- Rapid movement = 10,000,000 particles per minute

Common cleanroom contaminants include:

- Human hair
- Human skin flakes
- Dust
- Bacteria
- Mold

Other sources of cleanroom contamination:

- Water
- Air/ventilation
- Items being moved in/out of cleanrooms




Courtesy of Sandia National Laboratories

goes into a cleanroom must be designed to shed the minimum number of particles. Standard stationery and furniture do not meet these criteria, which means that everything, from pens to cleanroom furniture, must be specially designed. "The main indicators to consider are safety and suitability. Furniture needs to meet environmental conditions, whilst minimizing the introduction and generation of particles, as well as meeting Health and Safety and ergonomic requirements of operatives," says Govier. "It's important to remember the human aspect – there is a correlation between operator comfort, ergonomics and productivity. There have been some nice developments in this area, such as height-adjusted tables and cleanroom chairs made of cellular foam, which provides support for operatives, without expelling a lot of particles."

Getting cleaner

Is there room for improvement in cleanroom technology? Noland and Kaneps are both keen to see increased flexibility. "I'd like to see more modular cleanrooms. With standard cleanrooms, you invest a lot into one room but it is in one fixed location. As a contract manufacturer, we handle a large variety of projects and deal with lots of different processes. Flexibility is key. Although there have been advances in this area, I think more can be done," says Noland.

"There is definitely a greater focus on flexible designs," Holshouser agrees. "For example, flexible rooms with fixed utility stations in the ceilings and walls allow for processes to be moved and reconfigured into an optimal arrangement – and then reconnected as needed to the building utilities. This feature allows for the complete change in the function of a room."

It is also possible that the cleanroom of the future will not be a cleanroom. "When you get rid of people, everything in

All equipment, furniture and stationery in a cleanroom must be specially made so as not to generate particles.

Cleanroom classifications:

- Cleanrooms are rated depending on the number of particles per cubic meter
- A typical urban environment contains 35,000,000 particles per cubic meter
- The cleanest cleanroom is an ISO class 1 cleanroom, which can only contain 12 particles per cubic meter, which must be no bigger than 3µm

Data for infographic obtained from:

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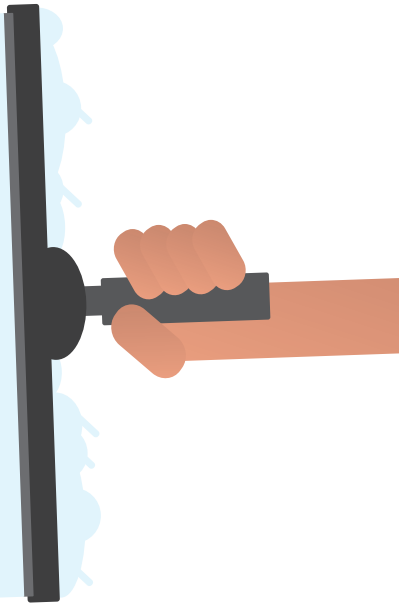

the cleanroom gets much simpler," says Rattray. "There is a move towards increasing the level of automation and robotics to improve quality and throughput, and minimize cleanroom personnel, but I think that the biggest advancement will probably end up being the elimination of the need for cleanrooms by implementing more closed processing areas in less classified space. Open processing areas are still constructed in clean spaces, but by creating less classified spaces, overall costs are greatly reduced."

For Govier, standards are a very important area. "At the moment there are many interpretations on achieving standards. A stand out moment for me was when I was on a site and saw a group of visitors being shown round a cleanroom. Instead of mop caps, they were wearing those blue plastic overshoes. Aside from the comedy effect of looking like extras from Thunderbirds, many of them had exposed hair, which is a huge contamination risk."

Right now, most companies seem more concerned about hitting the regulatory bar rather than leaping over it – and investments in new technology can be difficult to justify. But as simple as cleanroom technology is, when it fails, the consequence are dire. "There have been a number of well-publicized aseptic problems," says Kaneps. "Often, problems occur when a cleanroom is old and investments haven't been made. It's very expensive to retrofit a cleanroom environment, but the danger is that you can be outdated as new requirements come up."

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Room for Improvement

Today's cleanrooms may meet current quality standards, but what about the future? Opportunities for improvement can be found in all areas, from gowning to cleaning to implementing robotics technology.

By Jeanne Moldenhauer and Brian G. Hubka

We recently came across a survey that asked, how has cleanroom technology and environmental monitoring changed? And the more we thought about it, the more we realized that not a lot has changed.

It's well-known that the pharma industry does not like to rush into change, but it's also true that advances have been made in contamination prevention technologies that could provide improvements in pharma's cleanrooms. Perhaps one of the biggest advances to impact cleanrooms is the development of isolators and restricted access barrier systems (RABS). However, even the adoption of this technology has been painfully slow in pharma compared with other industries. Adopting new technology always involves upfront costs – and cleanroom downtime, which can be problematic, and pharma companies also have a habit of being wary with any new technology. It is true that some new technologies may have teething issues. For example, there have been concerns with leaky isolator gloves. However, we have also seen advances to address this, such as rubber materials manufactured in Asia that are designated "leak-proof." In time, perhaps these materials will see greater use in the industry.

In this article, we aim to give a short overview of some of the ways in which cleanrooms could be improved. Writing about each area in depth would fill a whole magazine a dozen times over, but perhaps these pointers will encourage you to dig a little deeper.

Dressing the part

Humans are the biggest sources of contamination in a cleanroom (1). The outer layer of the human skin alone can host more than one million microorganisms per square centimeter (2). Gowning helps to prevent these microorganism from reaching the cleanroom and is a relatively easy area to invest in compared with infrastructure changes. However, garments can only minimize the chances of contamination; it is almost impossible to completely prevent it.

The gowning area is where operators change into their cleanroom garments. Gowning procedures will vary from company to company (and depending on the class of cleanroom), but over time, the gowning area itself can become contaminated. There are a number of technologies that could be used in gowning rooms. First of all, lockers, benches and other surfaces could be painted with antibacterial and antifungal paints; many of these

paints use nanoparticles (for example, silver) that are antifungal and antibacterial.

Most cleanrooms require people to wear gowns/overalls, shoes (or covers), hairnets and goggles. If you look at gowns offered by vendors, you'll see that there have been numerous advances in gowning materials – many of which are based on nanotechnology – to create non-shedding garments. There are materials that keep moisture in, keep moisture out, are antibacterial or antifungal (or both), keep odors in, are water and stain resistant, difficult to rip or tear... the list goes on. New methods for folding and packaging gowns have also been developed that can reduce risk. For example, some vendors fold their gowns in a way that reduces the likelihood of the outside surface touching the floor during donning of the uniform.

Ask yourself when the gowns in your cleanroom were last updated. Never?! Remember that gowns are getting smarter all of the time. Some even incorporate RFID chips that track the frequency of washing cycles.

Shoes can be a problem in a cleanroom. Shoes can be a significant source of contamination because shoes travel everywhere. Some companies still use shoe covers, but contamination can pass to gloves, hands or other areas when donning the covers. And the covers themselves can also come loose (I've seen a visitor to a cleanroom facility walking around with a shoe cover half on, half off more than once). Some companies issue plant shoes for employees to wear, but these shoes can still make it into the cafeteria or elsewhere in a facility. Some pharmaceutical applications utilize rubber boots that can be worn over shoes, but they can also be a source of contamination if they are not routinely cleaned and disinfected. In fact, various sterilization and decontamination methods exist, such as chemical disinfectants, but they are rarely employed simply because most people just don't understand the risks. Goggles are usually sanitized with ultraviolet light, but chemical sterilants, such as ozonated water, can be used, or nanomaterials can make them "self cleaning." This could also reduce the risk of contamination.

Wash your hands!

The link between washing hands and hygiene has been known since the 19th century (3). And those of us working in cleanrooms today know that we should wash our hands for at least 20 seconds, but we suspect that few follow the full procedure. Luckily, there are ways to clean hands faster; for example, using ozonated water can shorten the time needed to eliminate contamination present on skin. Ozonated water also is effective at ambient temperatures, which makes it useful for areas where hot water is in short supply. It's one example of something that has been used for years in the food services industry, both for employee hands and the foods themselves, but is not well used in the pharma industry.

Once hands are washed, they must be dried. Some companies prefer to use cleanroom-safe paper towels, others cloth towels, and then there are air dryers. Many believe air driers are better for contamination control, but a recent study claimed that a common type of air hand drier spread more germs than paper towels because it propels the bacteria into the air (4). All drying methods can lead to additional sources of contamination, so it is important to recognize the strengths and weaknesses of the system you choose to use and to mitigate the risks. Whatever solution you choose, you must ensure that employees follow procedures.

"Making changes to an actual cleanroom facility is more difficult than updating gowning materials."

Facility makeover

Making changes to an actual cleanroom facility is more difficult than updating gowning materials. New cleanroom facilities are being built all of the time, which gives the opportunity for improvement, but there are also a number of existing, well-established cleanrooms with stainless steel infrastructure. Many old cleanrooms are still compliant with regulations, but others can run into problems. An example of this was seen in 2015, when the FDA identified sterility problems at the Clinical Center Pharmacy of the National Institute of Health. Garment-related issues were identified, such as protective apparel not being worn as necessary, but there was also an observation about the facility design: "Specifically, facilities were not designed and controlled to prevent contamination risks… there is inadequate separation of the aseptic processing area from the common pharmacy." (5)

In light of this, it's always worth reviewing an older cleanroom for potential problems and to evaluate if new advances can help.

Isolators and RABS have been in existence for many years, but it's incredible just how few companies have actually installed these systems in their sterile operations in the United States – leaning towards the 'if it ain't broke, don't fix it' mentality. Many companies will not spend the money if their current system is already compliant, even if it is not the most efficient. In our experience, we've found that Europe and Asia have been ahead of the US when it comes to implementing these technologies, particularly when it comes to building new facilities.

Likewise, single-use systems are not as readily used as one would expect, even though such technologies have the benefits of being purchased sterile, used for one production batch, and then discarded, eliminating the need for cleaning. Although single-use is

Top Cleanroom Advances

Tim Sandle is the head of microbiology at Bio Products Laboratory (UK) and a tutor at the University of Manchester, specializing in microbiology, cleanrooms and sterilization. According to Sandle, one overriding concern with cleanrooms and cleanroom technology is maintaining product or operator protection. The drivers for developing cleanroom technology are to increase the level of protection or to decrease operational costs – but it is crucial that the latter does not impinge on the former. Here, Sandle gives a rundown of his top advances in cleanrooms in recent years.

Design

It is important to dedicate time to designing cleanrooms and the equipment located in cleanrooms. If there is a design fault at the conception stage, it will be expensive and time consuming to rectify. Modern cleanroom design uses computer-aided engineering progams, such as Building Information Modeling (BIM) software, which covers geometry, spatial relationships, light analysis, geographic information, quantities and properties of building components. Cleanroom design should also form part of the broad 'Quality by Design' initiative.

Construction and the modular concept

Recent advances in construction ensure that cleanrooms are built to a higher standard in terms of reducing contamination risks. For example, plasma welding can be used for potentially weaker areas, like ventilation ducting, to ensure improved leak tightness (a leak of air from a less clean area into the cleanroom is a major contamination risk). Another development is the use of 'double skin' constructions around air-handling units, which also minimizes air leakage.

Traditional cleanroom design is sometimes described as "hard-walled" or "hard-lidded." Softer walled modular designs are a more recent development. Modular cleanrooms offer the advantage of fast construction, normally at a lower cost, and allow users of cleanrooms to expand their clean area footprint relatively easily, which explains their popularity. Modular cleanrooms also offer more flexibility – and flexible designs are important, especially for small-scale or emerging technologies, such as biotechnology.

Isolators and RABS

A key advancement in cleanroom technology, in terms of contamination control, is barrier technologies, such as isolators and restricted access barrier systems (RABS). In areas, such as aseptic filling of sterile drug products, such technology is being adopted to replace conventional cleanrooms. Isolators and RABS restrict operator access to the most critical areas of machinery. Of the two, the isolator provides the most complete barrier and is the superior technology. Arguably the most important contamination control step is the decontamination of the isolator environment. Here, the use of vaporized hydrogen peroxide (VHP) is the most common method.

Robotics

Given that human manipulations and interventions in the critical zone within the clean space represent the greatest risk, reducing the need for human intervention to the lowest possible level is an important part of contamination control. To a degree, this can be achieved with automation and robotics. Robotics is still in its infancy but can provide many benefits. As well as reducing human interaction, robotics ensure that activities are undertaken in a consistent manner and also provide a means of adapting the mechanical operation to suit the filling of different types of products. If designed correctly, robotics will not generate a high level of airborne particles and can be sanitized using disinfectants.

Energy conservation

There have been a number of global initiatives around energy efficiency in cleanrooms, such as the EN 16001 standard. Energy efficiency provides a means for cleanroom users to meet energy targets and save costs. Advances in microcomputing also allow the motors that drive cleanroom air conditioning systems to be dynamically self-adjusting, whereby the airflow adjusts in relation to changes in pressure or to the filter loading (particle challenge).

Antibacterial materials

An important preventative measure for contamination control is the use of antibacterial materials to coat cleanroom surfaces (sometimes referred to as "biotrunking"). Such surfaces include stainless steel, where silver or copper can be introduced into the steel surface. An advantage of silver ions is that, although they have antimicrobial properties, they are rarely toxic to human cells.

now well established in biopharma manufacturing, it is very much underused by generic and small-molecule drug manufacturers. There are benefits to using single use in a cleanroom, even for non-biopharma drugs. For example, it is possible to save all containers until batch release, so that if you believe a contamination event occurred at a particular stage of the process, you can sample the single-use system used to confirm or deny any contamination.

Robotics are used in many manufacturing industries for picking, placing and packing – and can also be fitted with camera systems to allow operators to see the process (remotely, in some cases). Robots are making their way into the pharma industry, most notably in terms of lab automation and drug discovery (robots can screen thousands more potential drugs than any human can), but they are also increasingly found in cleanrooms and have the huge benefit of almost completely eliminating human intervention – and the potential for contamination. However, we don't believe that robots are being used as much as they should be – and they are certainly capable of so much more. One growing application in the industry is using robotics for filling RABS units.

Every little counts

Investing in new technology is not the only way to improve a cleanroom. What about using antifungal sprays on walls and surfaces? Sprays can coat the surface, forming a hydrophobic barrier that attracts – and kills – mold spores. Depending upon the cleaning regimens used in these rooms, the sprays can be effective for a year or more. Importantly, don't forget your air ducts. Air ducts are notorious for harboring mold spores and antifungals can make a big difference. As an industry, we tend to trust HEPA filters to remove these, but small sections of mold have been shown in studies to pass through a typical HEPA filter and, given the right conditions, subsequently grow in the cleanroom. Antifungal paints can also be used on floors and walls.

When it comes to cleaning, pharma companies like to stick with tried and tested. But the area of cleaning and disinfection has seen many advances and many newer options are not used – or even known about – because most companies haven't considered an alternative. The problem with many current cleaning methods is that they can leave residue, which some operators mistakenly believe is a good thing because it means the product is "still disinfecting." Residue should be removed with specialist paper towels based on nanotechnology. There are also towel wipes that are designed to "rejuvenate" stainless steel surfaces, making them look new. And though it may simply sound like an aesthetic problem, recently there has been a lot of regulatory focus on the famous black, brown, rust-like or mold-like particles.

It's quite easy to be innovative when it comes to cleaning products in the pharma industry; after all, many new technologies aren't typically used in pharma's cleanrooms, including hydrogen activated water, ozonated water, chlorine dioxide and nitrogen dioxide – all of which achieve the right level of sterilization without leaving a residue. It's not as difficult as you might expect to change cleaning and disinfecting procedures; all that is required are some effectiveness studies.

Environmental monitoring is another area ripe for improvement. For the most part, the pharma industry uses microbiology lab methods that have changed very little since the days of Pasteur and Koch. Recently, rapid and alternative microbiological methods (RMMs) have emerged but uptake in the industry has been slow (6). Today, RMMs tend only to be used sparingly for training or for supporting investigations. In most cases, RMM results can be obtained in real time or near real time. The cost of RMM technologies is falling and in our opinion, RMMs will see better uptake in the cleanrooms of the future.

When it comes to environmental monitoring data, there are many tools available, from control charts to standard limit tests to contamination control rates. Vendors have developed automated systems to monitor and assess environmental data, and though some of these are expensive, there are now a number of cheaper alternatives. It's surprising how many companies are still using spreadsheets and home-grown databases...

The effort that goes into environmental monitoring is also up for debate. Many operators performing routine environmental monitoring in well-kept facilities are used to seeing zeros on plates in aseptic areas. And yet the current level of monitoring must be maintained. If environmental monitoring was truly risk-based, then it would make sense to reduce the type of monitoring conducted... The subject of environmental monitoring is a whole article unto itself (as are all of the topics discussed here).

We hope we have shown that there is much more that can be done to improve your cleanrooms – and in some cases, all that's needed is an open mind and an eye for detail.

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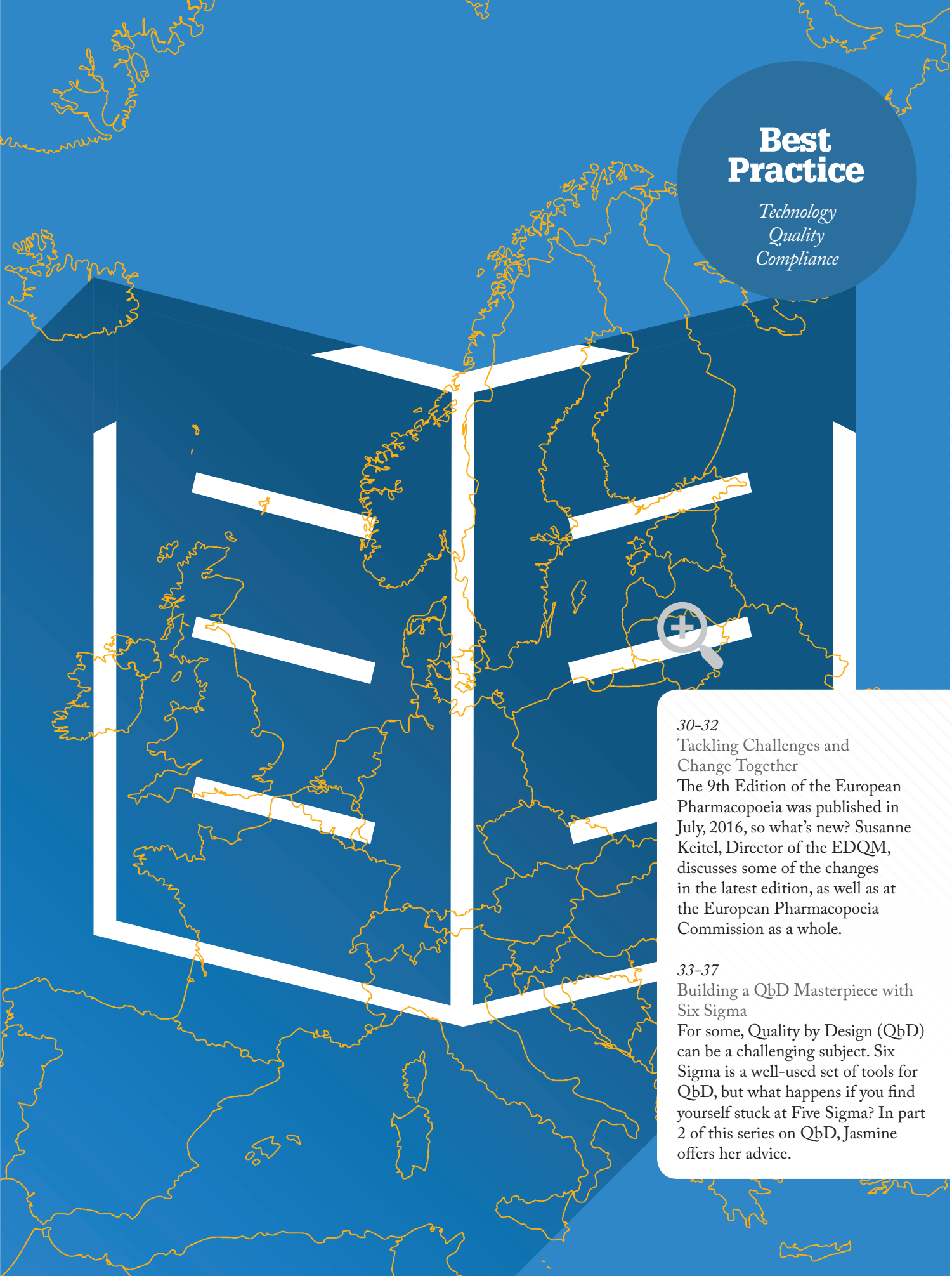

Best Practice

Technology
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Tackling Challenges and Change Together

The latest edition of the European Pharmacopoeia was published in July 2016 and some large changes are afoot. The industry is more globalized than ever before, and a greater range of international experts are being encouraged to get involved with setting and maintaining standards.

By Susanne Keitel

Setting public standards for medicinal products in Europe has come a long way over the past 50 years. The 1st Edition of the European Pharmacopoeia (Ph. Eur.), published in 1969, comprised a modest 120 texts. The 9th Edition of the Ph. Eur., published in July 2016 – and due to become legally binding in 37 European countries and the European Union as such on January 1, 2017 – contains some 2,300 monographs and more than 350 general texts.

But the numbers only tell part of the story. Collaboration has been the key from the very beginning. Today, there are 37 member states of the Ph. Eur. Convention and the EU, 28 observer states and organizations, and 700 or so experts in every field of the pharmaceutical sciences – all volunteers – who participate in more than 70 groups of experts and working parties. Each and every one of them makes an invaluable contribution to setting Europe's legal and scientific benchmark for pharmacopeial standards.

This collaborative result, however, is not a linear process; rather, it is a dynamic, complex interaction of all parties involved.

In this article, I will focus on recent changes in the work of the Ph. Eur. Commission and the European Directorate for the Quality of Medicines & HealthCare (EDQM). The Ph. Eur. is published by the EDQM, which enables the development, supports the implementation and monitors the application of quality standards for safe medicines and their safe use. The activities of the EDQM include providing the scientific secretariat to the Ph. Eur. Commission, which is composed of delegations of the 38 signatory parties. The Ph. Eur. Commission is responsible for the development of new monographs and general texts, as well as the revision of existing texts. The EDQM also regularly organizes consultations, meetings, webinars and other events with stakeholders to ensure that the Ph. Eur. remains relevant to industry and its other users.

Given the daily impact of globalization on pharmaceutical activities in specific geographical zones, regulators and standard setters worldwide are actively seeking to exchange information and collaborate in areas where international harmonization of standards makes real sense. With this in mind, the Ph. Eur. Commission has made some changes recently that I think are very relevant and interesting for stakeholders.

Opening doors

In November 2015, the Ph. Eur. Commission decided to revise its working procedures to allow experts from outside of Europe to become further involved in its work. Traditionally, experts wanting to get involved with the Ph. Eur. had to be nominated by a member state. However, the reality of today's pharmaceutical environment is that it is becoming increasingly globalized. To take just one example; more than 80 percent of the active pharmaceutical ingredients used in medicines for the European market today are produced in countries outside of Europe and the US. It is also no coincidence that the Ph. Eur. is recognized and used in more than 100 countries worldwide – and not only in the Ph. Eur. member states.

This decision to bring in experts from all over the world is a significant one for us, and I believe it will ensure that the Ph. Eur. is even more representative and encompassing of worldwide developments. Experts from non-Ph. Eur. member states and non-observers states can now be nominated for the Ph. Eur.'s groups of experts and working parties, which are crucial in the ongoing elaboration and revision of the methods and texts of the Ph. Eur.

"This decision to bring in experts from all over the world is a significant one for us."

In aiming to make it easier for important potential contributors to become involved, we have also removed the limitation of one member state expert in a group and simplified the process for nominating ad-hoc specialists to support the work of the Ph. Eur.

As a next step, the Ph. Eur. Commission recently launched a worldwide call for experts ahead of the next session in November, when all the members of the current groups of experts and working parties will face

re-appointment (which happens every three years). At the moment, health authorities, industry and academia each provide approximately one-third of participants.

These recent changes have also influenced the structure and focus of the EDQM's upcoming conference in Tallinn (Estonia) on September 27-28. To mark the publication of the 9th Edition of the Ph. Eur., the EDQM is organizing a major international conference: the European Pharmacopoeia: Tackling Future Challenges of the Quality of Medicines Together. The main focus of the conference will be workshops dedicated to four key topics: new technologies; the control of elemental impurities (i.e., the impact of the ICH Q3D Guideline); setting pharmacopeial standards for biotherapeutic products; and excipients, other components and international harmonization.

The four workshops are intended to provide a platform for the exchange of experience and opinions – and the feedback will help the Ph. Eur. Commission and EDQM to define their priorities across the board for the next three years. The chosen topics are reflected in the revisions and new additions to the 9th Edition of the Ph. Eur. In terms of new technologies; for example, the Ph. Eur. is the first pharmacopeia to include a general text on the application of chemometric methods to analytical data. However, I think that the workshops on the control of elemental impurities and on setting pharmacopeial standards for biotherapeutic products are particularly important.

Addressing elemental impurities

Preparations are in hand for the implementation of the ICH Q3D guideline on elemental impurities, which covers the evaluation of toxicity data for potential elemental impurities, a permitted daily exposure for each element of concern, and the development of controls to limit the inclusion of elemental impurities in finished drug products. The Ph. Eur. Commission has decided to reproduce, in the current general chapter 'Metal catalyst or metal reagent residues' (5.20), the principles set out in the ICH Q3D guideline. As a consequence, the current general method 'Determination of metal catalyst and metal reagent residues' (2.4.20), which describes the general approach for the determination of metal catalyst or metal reagent residues in substances for pharmaceutical use, will also be revised.

The Ph. Eur. Commission intends to introduce a cross-reference to revised general chapter 5.20 in the general monograph 'Pharmaceutical preparations' (2619), thus making application of the ICH Q3D guideline legally binding for all medicinal products within the scope of ICH Q3D. This revised general monograph is expected to be published in Ph. Eur. Supplement 9.3 on 1 July 2017; chapter 5.20 will become legally binding as of January 1, 2018.

A revised version of the general monograph 'Substances for pharmaceutical use' (2034) has also been published for public comment and has been revised to clarify how to handle substances used in pharmaceutical products outside the scope of the ICH Q3D guideline. It is also expected to be published in Ph. Eur. Supplement 9.3.

Already, the 9th Edition contains 760 individual monographs that have been revised to delete the reference to the general chapter Heavy metals (2.4.8). The revised monographs cover substances for human use only and for human and veterinary use, but not substances for veterinary use only.

The biotherapeutic discussion

I see the biotherapeutic product workshop

International Cooperation

Globalization and expansion in international trade are driving a growing need to develop global quality standards for medicines. In addition to providing a vital instrument for registration, market surveillance, and the free movement and trade of medicines among as many countries as possible, harmonization also serves to reduce duplication of testing and reporting during drug development and quality control.

International cooperation has always been a vital part of the Ph. Eur.'s work. In fact, the Ph. Eur. itself is a perfect example of the benefits of collaboration and work-sharing, given that it has resulted in continent-wide harmonized quality standards. In 1989, the Ph. Eur., the United States Pharmacopoeia and the Japanese Pharmacopoeia formed the Pharmacopeial Discussion Group (PDG), with the purpose of harmonizing pharmacopeial standards (excipient monographs and selected general chapters) in these three regions. The PDG also works closely with what is now the International Council for Harmonisation (ICH) in collaboration with regulators and industry.

The Ph. Eur. is actively involved in a number of other international harmonization initiatives, such as the World Health Organization (WHO) initiative to draft "Good Pharmacopoeial Practices" (GPhP), which may serve as a basis for future work-sharing and collaboration amongst pharmacopoeias worldwide. The International Meeting of World Pharmacopoeias is also organized under the auspices of WHO, with the aim of bringing together the different pharmacopoeias and discussing potential ways to strengthen collaboration and harmonization, for example, via the elaboration of the GPhP.

as a great forum for stimulating, controversial and productive discussions. Following the approval of recombinant human insulin in 1982, which was the first biological derived from recombinant DNA technology, more than 200 biotherapeutics have received regulatory approval in Europe. Ph. Eur. quality standards have been elaborated for many of these first-generation biotherapeutics, such as peptide hormones, growth factors and interferons. Traditionally, these monographs have been elaborated using data submitted by several manufacturers of products authorized in Europe (this is known as the 'multisource approach').

Other first-generation biotherapeutics – such as interleukins, coagulation factors and monoclonal antibodies – have recently faced (or will face) patent expiry in the near future, which reinforces the need for public standards. This is also the case for second-generation biotherapeutics, a class of modern biological substances that have undergone engineering to alter their pharmacological activity. To make standards for this latter class of biotherapeutics available at the time of their patent expiry, we have developed an alternative mechanism for elaborating Ph. Eur. monographs, developed in close collaboration with single manufacturers (the so-called single source or "P4" approach). This alternative mechanism has been a pilot project since 2008 and will be completed at the end of 2016. In the June 2016 session, the Ph. Eur. Commission concluded that the work performed during the pilot project has successfully proven that it is possible to use this single source approach – and that it is extremely useful for elaborating public standards for complex biotherapeutic molecules, while at the same time providing flexibility in their requirements to allow for the future development of products. However, a number of stakeholders have their reservations against this approach so the Tallinn conference, especially this workshop, will provide a timely forum for exploring the shades of opinion on this very important question.

Discussions such as these are crucial for preparing for the future and maintaining the relevance of the Ph. Eur. in the ever-changing globalized pharmaceutical environment. By continuing to work together with experts from national and European authorities, universities, scientific institutes and industry, and by taking concrete steps to ensure the participation of experts from around the world, I believe that the Ph. Eur. is well-prepared for the future.

Susanne Keitel is Director of the EDQM. You can read a Sitting Down With interview covering Susanne's career on page 50.

Get Involved

Becoming an expert in the groups and working parties of the Ph. Eur. means you have the opportunity to shape the texts at an early stage, as well as the chance to network with other scientists, and expand your knowledge of the Ph. Eur. and the European regulatory system. Experts are welcome from both inside and outside of Ph. Eur. member states, and from a wide variety of professional backgrounds.

More details about getting involved, including the nomination form, are available at: http://bit.ly/2alyhqf.

Building a QbD Masterpiece with Six Sigma

Are you stuck at a Five Sigma improvement project? Or is Quality-by-Design based product development too cumbersome? Many people struggle with QbD, but there are secrets to success.

By Jasmine

In the May issue of The Medicine Maker, I wrote about "The Beginning of the End of Quality by Design" (http://bit.ly/27QT4Iz). I described the history of how Quality by Design (QbD) came about – and why there may come a day when the concept is so deeply entrenched in pharma manufacturing that it no longer exists. But we are certainly not at that point yet and to get there, we need to accelerate the use of QbD. A well-used – and excellent – set of 'tools' for QbD is Six Sigma. The term 'Six Sigma' was coined by Motorola in the 1980s, and involves using a data-driven methodology to reduce variability during manufacturing, resulting in process improvements.

The Five Sigma barrier

In less than two years after Six Sigma became established in manufacturing in Motorola and GE, practitioners found themselves at a point where the opportunities and improvements they suggested using Six Sigma started becoming too expensive. They had encountered the "Five Sigma Barrier" (1), which equates to 233 defect parts per million, versus Six Sigma, where there would be no more than 3.4 defect parts per million opportunities (99.9997 percent error free). Six Sigma revolves around improving existing processes, but there can be limits to the level of improvement possible. Eventually, improvement efforts reach a point where the cost starts negating the anticipated financial merit. With an existing process, certain features will be inherent. For example, if the design was not well defined at the outset there may inadvertently be limitations, or even quality issues, designed into it. Even if the design flaws are identified prior to product launch, they cannot always be rectified easily – the later in the development cycle they are discovered, the more costly they are to correct (2). Sometimes, the only option is to redesign the product, which can be too costly or too late in the product lifecycle.

Some manufacturers may be content with Five Sigma, but many strive for the near perfection offered by Six Sigma, particularly in the pharma industry where quality is crucial. Six Sigma has traditionally been driven by the popular DMAIC methodology (define, measure, analyze, improve, control) and has focused on continuous improvement of an already existing process. DFSS uses the DMADV (define, measure, analyze, design, verify) methodology (3) to create new processes and is used when no process exists, or when an existing process has already been optimized through DMAIC and still does not meet the required level. In other words, if you have hit the Five Sigma barrier, then DFSS can help you break through.

The aim of DFSS is to clearly understand the requirements at the outset and then to design a process that is highly capable of meeting or exceeding those requirements with minimal variation. DFSS also provides the tools and a structured approach to efficiently create these new processes by helping to minimize the effort, time and costs required to design and eventually manufacture the new product on an ongoing basis. The fundamental premise behind DFSS is that to effectively achieve these goals, we must thoroughly understand the process and product so that we can identify and appropriately control critical material and process parameters. The DFSS toolbox has a wide variety of tools and methods, some of which are shared with the conventional Six Sigma methodology of DMAIC.

Joseph Juran, the originator of QbD, distinguished "quality improvement" from "quality planning": improvement is concerned with solving existing problems; planning is concerned with shutting down the hatchery that creates those problems in the first place. In the pharma industry, we know QbD as a systematic approach to development that starts with predefined objectives, and emphasizes product and process understanding, as well as process control based on sound science and risk management. The DFSS methodology and toolbox fits neatly into the QbD framework of developing robust products with good process understanding (see Figure 1).

Many Six Sigma tools are used in the pharma industry at different stages during the product's lifecycle, such as Design of Experiments and Control Charts. The tools described in this article are from all stages of the DMADV cycle. I have selected tools with the greatest relevance and potential for pharmaceutical applications, as well as their current usage status. However, they don't necessarily need to be used in the stages described below for all products and processes. Exactly how they are used ultimately depends on you!

Define phase: quality function deployment

In the beginning of QbD-based development, pharma scientists build a Quality Target Product Profile (QTPP) for patients to build quality, safety and efficacy into the product (4). A quality function deployment (QFD) made in the beginning of product development helps focus on the requirements of multiple stakeholders; not just patients but different regulatory agencies, business targets, manufacturing sites and supply chain partners. Part of QFD is the House of Quality. Many free templates for creating a House of Quality are available online, and the aim is to

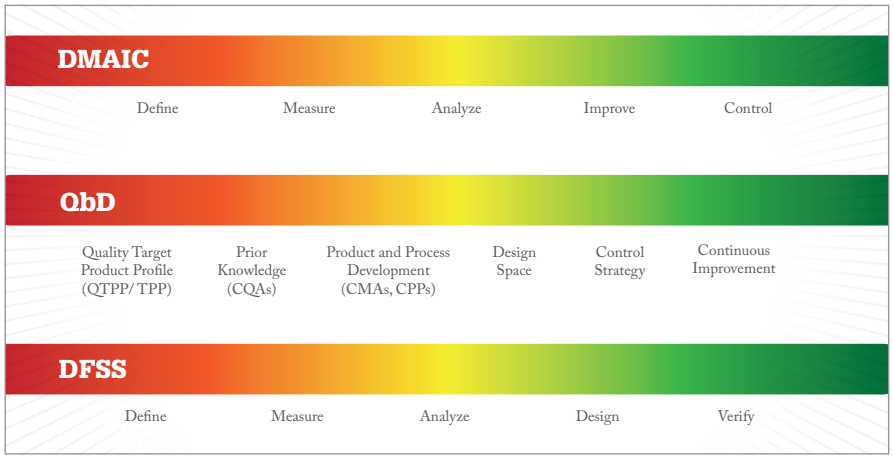

Figure 1. Juxtaposing the DMAIC, QbD and DFSS methodologies.

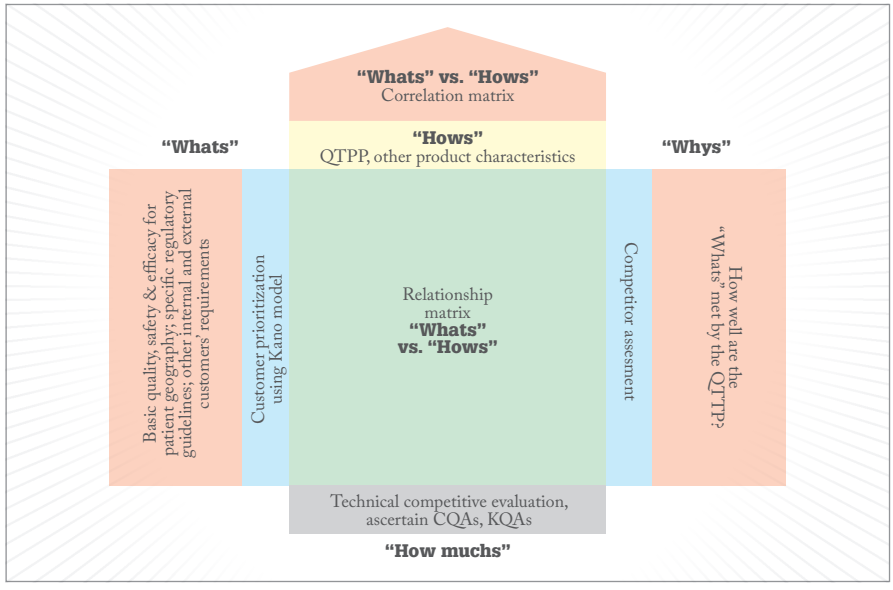

Figure 2. A House of Quality in a QFD.

correlate desired aspects of the end product with specific processes and specific business outcomes. Figure 2 is an example of a very simple House of Quality.

- The "What" section on the left is the door to the house and should include all of the aspects desired in the final product. The Kano Model (explained later) can be used to build the customer prioritization scale, which is the blue window section on the left. In other words, what are the most important aspects?
- The yellow "How" section is the set of product characteristics that would meet the customer's requirements. As an illustration, a regulatory requirement of efficacy may be met by different in vivo studies and a business requirement of cost per unit may be met by a defined process yield.
- The relationship matrix is the main room in our House of Quality. This is where "What" meets "How". This is a quantitative risk-based assessment and a pre-defined scale to show how well the chosen product characteristic describes the customer requirement.
- The roof of the house is the correlation matrix. This section suggests inter-relationship between the product features. These inter-relationships can ease and hasten product development, and facilitate investigations in case of failures. As an example, product characteristics, such as moisture content and endotoxin level, may have a complementary effect on one other, so controlling moisture content through shelf-life would be one way to ensure an endotoxin-free product.
- The "How Much" section is the foundation of the House, and is the sum of the product of the "What" and the "How" for each product characteristic. It should be a risk-based assessment for the product developer of what is most critical for product success. It is in this section that the critical quality attributes (CQAs) for the patient can be identified and other key quality attributes for the business can also be seen here.
- The "Why" section on the right side of the house includes a window of competitor benchmarking; for example, if you're developing a generic product you may wish to look at the innovator. In this section, the performance of the proposed product can be compared with that of competitors to understand what features need to be emphasized. You should also examine the performance of necessary features. For example, in the case of a generic product, specific characterization studies may be necessary to distinguish the in vivo performance from that of competitors, or to prove similar performance to that of the innovator.
- The door on the right is the back door and is a final assessment to check that all customer requirements have been adequately met by the first level of quality planning for product characteristics.
- After building your first House of Quality, it will cascade into a whole estate of houses. As an illustration, critical material attributes of raw materials, in-process CQAs and critical process parameters (CPP) can be built in subsequent Houses

of Quality. It may sound obvious, but this is an excellent method for bringing QbD elements like QTPP, CQAs, CMAs (critical material attributes) and CPPs together. . It's also effective at encouraging people to think about different areas, such as getting development scientists to think about manufacturing. And it isn't just useful for defining product development at the outset; it can be used throughout a product's lifecycle.

Define phase: Kano model

A second tool that can be used for the define phase of DMADV is the Kano model. The Kano model was developed in the 1980s by Noriaki Kano, who is today a professor at the Tokyo University of Science. The aim of the model is to provide insight into product attributes that are perceived to be important to customers. Traditional ideas around quality assumed that customer satisfaction was simply proportional to how functional the product or service was. In the Kano diagram (see Figure 3), this proportional relationship is represented by the line passing through the origin at 45 degrees to the horizontal. But in reality, customer requirements are not one-dimensional; for instance, "wow" elements can also make an impact on a product's attractiveness. In pharma, of course, the final customer is the patient. A well-designed product is not only effective, but also helps patient compliance.

A good Kano assessment can help define product expectations at the very start of development, allowing you to prioritize the characteristics that will be most important to patients. To sum up, a Kano model can (5):

1. Set priorities for development by understanding the product characteristics that have the greatest influence on customer satisfaction via the QFD described above.
2. Provide valuable help in trade-off situations in product development.
3. Make it easier to custom-tailor solutions to specific problems.

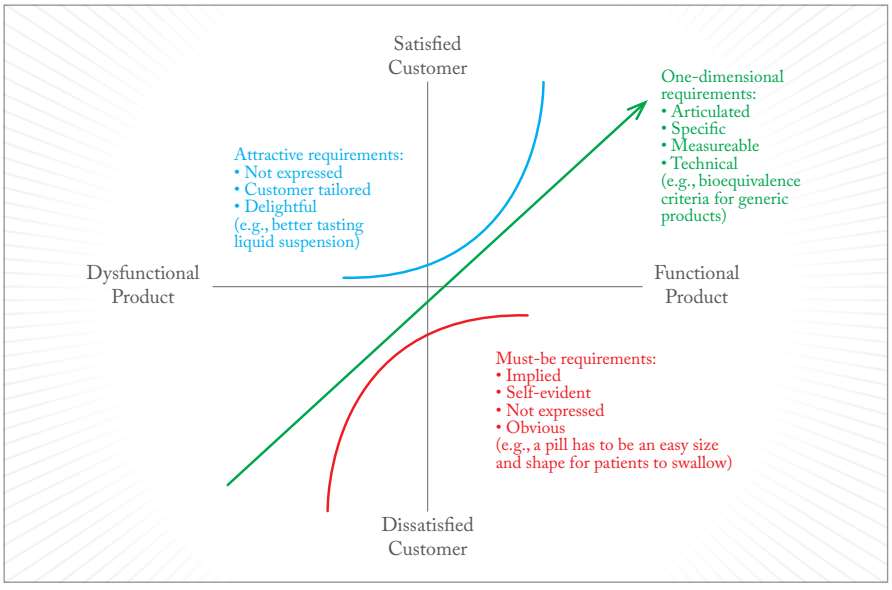

Figure 3. A typical Kano model

Moreover, discovering and fulfilling attractive requirements helps create a wide range of opportunities for differentiation.

At the beginning of this article, I mentioned that products can have inherent quality issues or limitations inadvertently built into the product. The define phase of the DMADV philosophy is crucial because it can avoid this issue and ensure that the right requirements are built in from the start.

Other development phase tools such as the Pugh matrix and the Hoshin Kanri method are also useful. A Pugh Matrix can help scientists in evaluating multiple ideas or design concepts against each other in relation to a baseline. Hoshin Kanri may be used after the selection of the right strategy for deploying and monitoring of resources. For further reading on these, I recommend reference 6.

Measure phase: design of experiments-based Gage R&R

While all analytical methods in the pharma industry meet prescribed ICH Q2 R1 standards for validation of analytical procedures, problems can arise (7). Here is one scenario that many of you may have encountered. An Analytical Method consists of an elaborate derivatized sample preparation. This sample has limited stability under stringent conditions. The sample is then prepared for analysis under a specific (also elaborate) preparation method. The sample is then analyzed using LC-MS. The method is validated, but the measurement system starts to throw up a few surprises. Ordinarily, a rivaling elaborate risk assessment is done, which helps to narrow the list of probable causes, and then a large list of risk mitigation measures are established for all these probable causes. Often, problems go away with such an approach, but this isn't always the case.

A design of experiments (DoE)-based gage repeatability and reproducibility (R&R) study can be used to tell you exactly how much of the method's variability comes from every one of the unit operations rather than setting acceptance criteria for each of them individually. Gage R&R is a statistical tool that measures variation in the measurement system. Using this tool means that when something goes wrong,

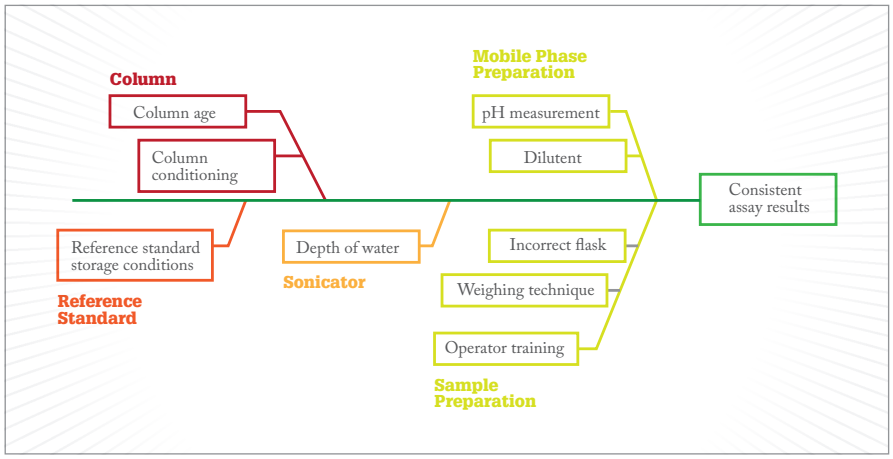

Figure 4. How not to make a Fishbone diagram.

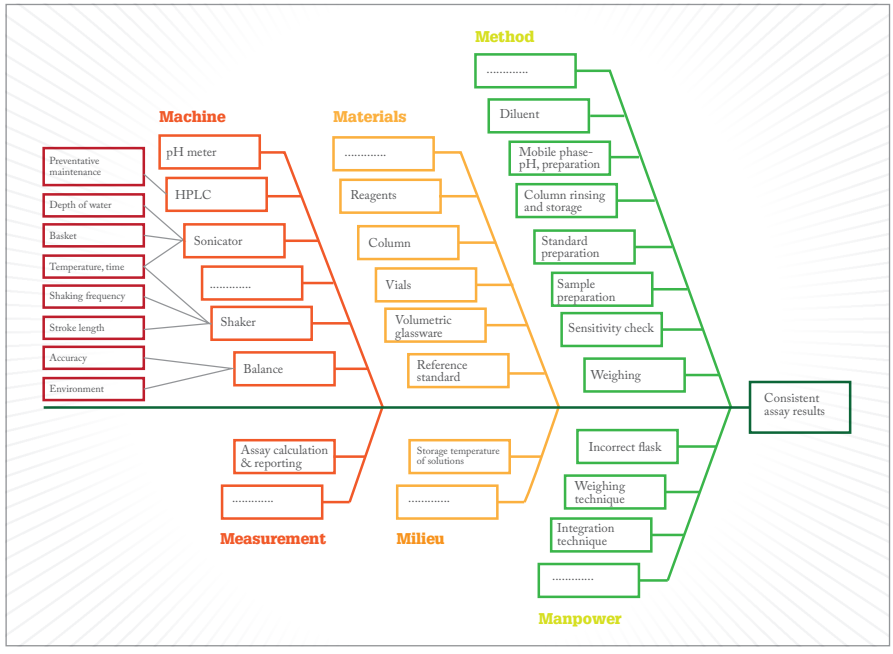

Figure 5. A better illustration of a Fishbone diagram.

an analyst will be able to identify a potential culprit based on sound science and statistical risk by the distribution of variance amongst all these unit operations. A multivariate approach is also an excellent way to check your method for its robustness and is now being encouraged by FDA Guidance on the topic of Analytical Procedures and Methods Validation (8). Results from Gage R&R also represent opportunities for continuous improvement in the lifecycle of the analytical method.

Analysis phase: fishbone diagram

Fishbone diagrams are commonly used in QbD-based development at multiple stages to identify potential causes of a problem. A Google search for "Fishbone Diagram Pharmaceuticals" yields many results similar to Figure 4, which is a fishbone diagram to identify what is critical to achieving consistently correct assay results. An effective fishbone diagram should go through the six (or seven) Ms: man, machine, materials, measurements, methods, milieu and, for some applications, management. Unfortunately, I find that it is common practice to simply put the usual suspects on a fishbone-shaped diagram, which is the case in Figure 4. Figure 5 shows a better fishbone diagram for the same problem. Analyzing all of the six Ms and their effect on the expected quality attribute can lead to a better understanding of all possible causes of variations for a process under development, as well as all the possible reasons why a quality attribute misbehaves during manufacture.

Design phase: Monte Carlo Simulation

Allow me to present a typical scenario in pharma manufacturing. Manufacturing requests specifications on process parameters for a new product from the development team. The development team doesn't really know what these limits should be. Realistic specifications are everyone's desire, of course, but with little knowledge of how to set realistic specifications, development usually opts to set specs so tight that they are guaranteed to work. Unfortunately, this makes life more difficult for manufacturing – and also, in turn, development. Each time a particular lot of product does not meet spec, manufacturing must ask development to help with investigations. The specifications may then be modified and eventually the specs are widened to realistic limits. Specifications should be robust, but also realistic. And it's better if you set them at the very start rather than using a back and forth approach.

The Monte Carlo method is a probabilistic technique based on generating a large number of random samples to simulate variability in a complex system. The objective is to simulate and test as early as possible to anticipate quality problems, to avoid costly design changes that might be required at a later phase and, more generally, to make life a lot easier on the shop floor. What is required?

1. a good Transfer Function (Y=f(X)) from design of experiments,
2. some knowledge about the distribution of data of the variables (Xs),
3. a little bit of adventure.

The result? Figure 6 – and an understanding of exactly how changes in Xs can affect Ys (9). This knowledge will

help you to confidently set specifications for Y given operating conditions, or the other way around – settings for parameters Xs to achieve Y with a prescribed performance.

Verify phase: process performance and capability indices

The final stage of DMADV is to verify or validate that the design will meet the intended needs repeatedly. When it comes to verification, the terms Process Capability Index (CPK) and Process Performance Index (PPK) are common. I have seen and used statistics a lot (and not just in the pharmaceutical industry), but when it comes to pharma, the amount of debate over the terms CPK and PPK is mindboggling!

It's easy to get caught up in the debates about what these values mean so here are a few simple points about what CPK and PPK represent.

- CPK represents the potential process capability (which is to say, how well a given process could perform in the ideal situation of no special causes of variability).
- PPK addresses how the process has performed without demonstration of process stability.
- In general, PPK is less than CPK.
- If there is a significant CPK–PPK difference, it implies that the process is not stable; thus, you will need to identify/eliminate special causes to reduce variability.
- CPK can be used to forecast future batch failure rate and PPK cannot (10).

Using PPK as a metric of performance at the development stage is not common, but it can be extremely useful in terms of setting a benchmark for the product's future performance. For example, if PPK is performed at the laboratory or bench scale, then assessing the feasibility of technology transfer and manufacturing performance becomes easier. However, I would like to point out that PPK requires corrections for smaller sample sizes, which can either be done statistically or by using higher number of samples (with caution) per batch.

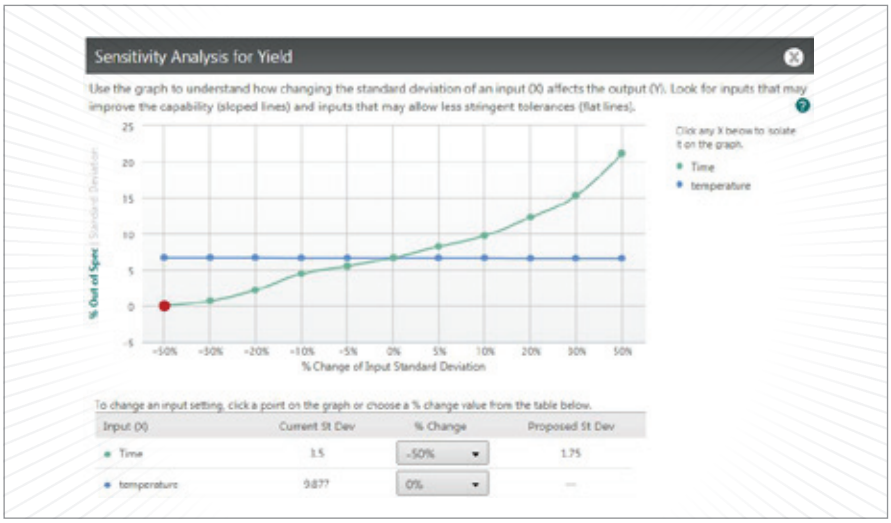

Figure 6. An illustration of a Monte Carlo Simulation using Minitab Devize.

Strive for the end

DFSS has been around for a long time now, but its use with QbD is not very popular yet. This may be attributed to DMAIC's popularity over DFSS, as well as the fact that any 'beginning' is always difficult. With no 'regulatory guidance' or publications suggesting the use of these tools, I am sure that several companies would think twice before including use of these tools in their dossiers, even if they were used in product development. This will change gradually as the relevance of these tools for business becomes clearer, with greater elucidations through articles like this.

So please go ahead; try out these DFSS tools and share your experiences. Together, we can drive QbD to its 'end'.

My next article will focus on the right ways to use statistics in the product's lifecycle.

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Finished Dosage Formulations Growth - A major addition to CPhI Worldwide

As UBM EMEA launches a new co-located event at CPhI Worldwide, 4-6 October, CPhI shares the findings from the recent roundtable debate on the global growth in finished dosage forms. The media/analyst briefing day gathered leading experts Jim Miller (PharmSource), Alan Sheppard (IMS Health) and Paul Fleming (BGMA) and members of the pharmaceutical media to discuss finished dosage formulations – everything from big pharma, contract manufacturers, to in/out-licensing and dossier specialists, end product distributors and generic pharma.
Chief amongst the trends reported was the increased need for different segments of the supply chain to work together in the creation of new patented drugs or value-added generics.

"Outsourcing for delivery systems is a key trend, as is partnering with more established companies in specific segments. For instance, if you only have a single oncology product, partnering and out-licensing with someone who has a wider dossier is a very good strategy."
Alan Sheppard, Principal, Global Generics and Biosimilars at IMS Health.

Licensing and partnerships are integral to growth because they allow market entry with lower risk, and capitalise on local knowledge to speed-up regulatory approvals and pricing processes.

The key technological challenge for both generic and patented formulations identified is access to new technologies – spray drying, micronisation, hot melt extrusion and nano formulations – which enable the creation of more advanced, bioavailable and patient friendly combinations.

Citing IMS figures, Alan Sheppard reported that, in the last 4-years, the USA (58%) and Europe (17%) have dominated growth in new speciality medicines – with the largest profit opportunities in smaller patient cohorts and speciality drugs, where there are still unmet patient needs. However, in generic formulations, although the US still represents 28% of growth, the pharmerging markets are really the driving force underlying this upwards trend with 58% of growth. Significantly, and perhaps due to patient concerns in these regions, branded generics in emerging markets, particularly in Asia, are strongly preferred – whereas in the developed economies, in-prescribing is most common.

Generic companies and CMOs are now reimagining what is possible – as access to new technologies opens up more opportunities for innovative development.

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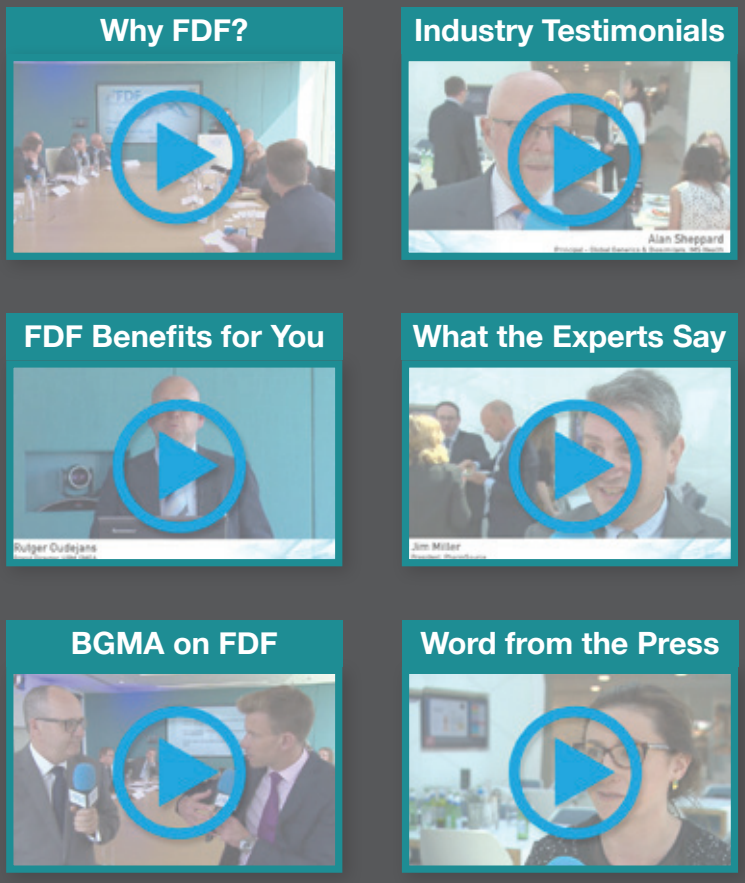

But collaborations are even stretching to excipient technologies says Jim Miller, president of PharmSource, as they help *"facilitate matrix and multi-particulate formulations – allowing increased bioavailability, all of which has put new demands on the performance of excipients."*

However, two major possible market challenges are the impending costs of GDUFA ii in the United States – particularly for CMOs with limited generics production. And, for generic companies, a longer-term question will be *"how to get a fair reward for incremental formulation developments,"* added Paul Fleming, Technical Director of the British Generic Manufacturers Association.

Collectively, there is a trend for governments, both developed and developing, to increase their use of generic drugs. And, with the drugs pipeline dominated by poorly bio-available compounds, a clear picture emerges that finished dose forms represent a tremendous opportunity for pharma companies, growing revenues at a breath-taking speed – both in emerging and developed markets.

In response to this, UBM is organizing an event that not only explores the key facts of the market, but also gives exhibitors and visitors the chance to source, analyze and connect with their ideal partners on a successful route to market.

Since its introduction at CPhI Worldwide in 2011, the Finished Formulation zone has grown rapidly to become the third largest segment of the overall event; totalling 11,000 square metres in 2015.

Developing this zone into a co-located event is a natural progression for the CPhI brand, which has evolved through its three decades from a small API event into the global meeting place for the entire pharmaceutical supply chain. By giving Finished Dosage Formulation its own voice, its own story, a vital platform emerges for people who haven't seen CPhI as their essential business event in the past.

Cara Turner, Event Manager Pharma at UBM EMEA, commented: *"We celebrate the launch of the new FDF event at CPhI Worldwide. This is the first time at a global level, that a networking, content and exhibition platform has been created specifically for finished dosage formulations.*

Looking ahead, we forecast this part of CPhI growing extremely quickly and envisage new audiences attending – there are natural synergies with diagnostic providers, licensors, delivery platforms and distributors, not to mention, it opens new avenues for existing audiences by widening the range of partners they can meet in one location."

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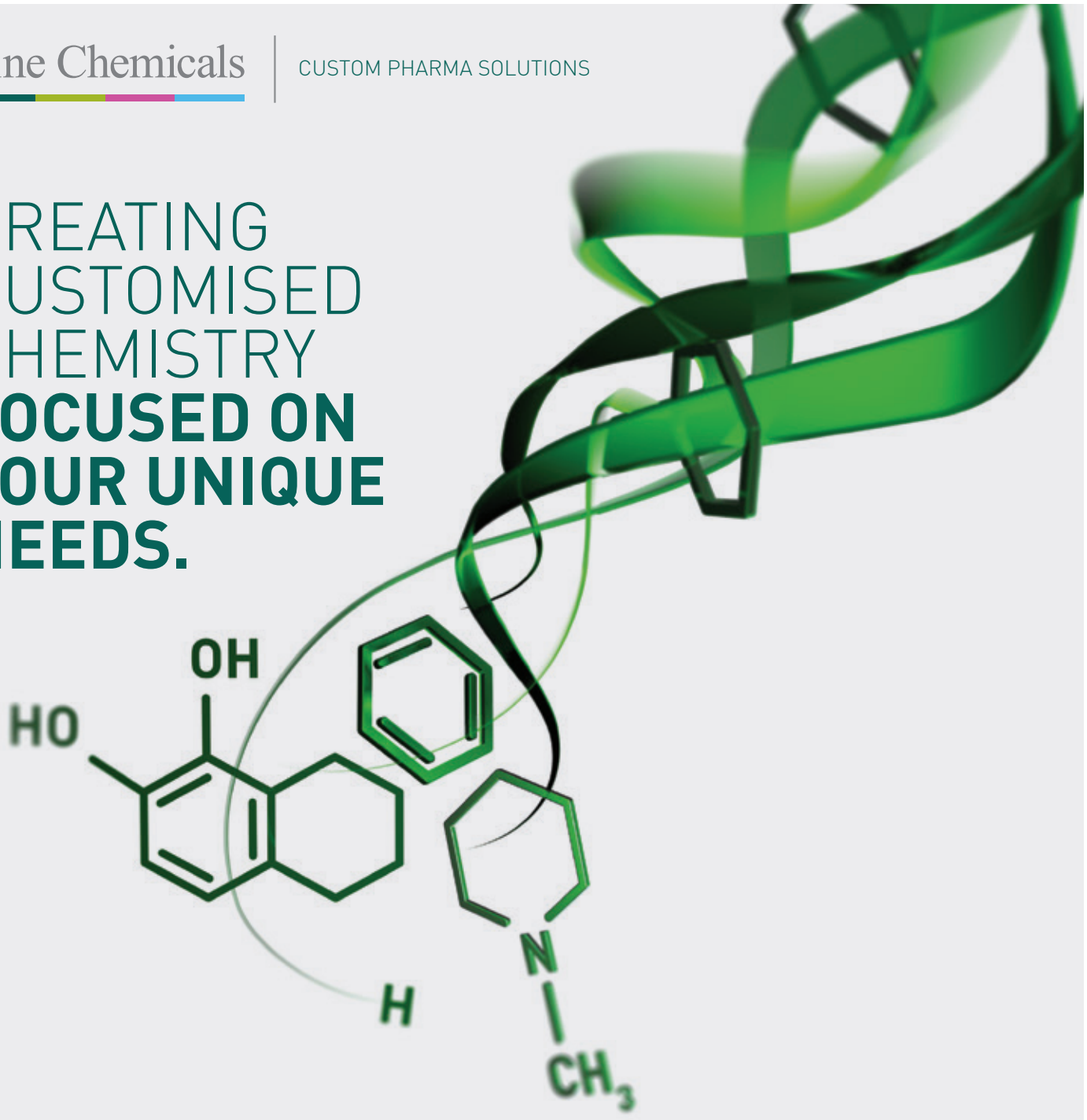

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The Soft Side of Drug Delivery

When it comes to oral drug delivery, tablets and capsules are often the "go-to" choice – but are you missing innovations in other areas as a result? The softgel is considered a good choice for poorly soluble molecules, and non-gelatin options are now broadening its reach.

December 2015 saw the launch of The Medicine Maker Innovation Awards, which recognized some of the most exciting technologies of 2015 (http://bit.ly/1ISQcS9). Catalent's OptiShell softgel technology was one of 10 winners.

At first glance, a new type of softgel may not seem like a startling innovation, but softgels are an important and proven drug delivery tool, particularly for poorly water-soluble drugs (of which there are an increasing number). The judges of the 2015 Innovation Awards praised the OptiShell technology for its focus on natural ingredients (plant-based rather than gelatin) and its ability to encapsulate higher melting point fill formulations.

Keith Tanner, manager of technology development at Catalent, was one of the first scientists assigned to work on OptiShell. Here, he shares the developmental story behind the innovation and explains why it was so important for the company to develop a non-gelatin based softgel.

The Softgel Story

As told by Keith Tanner

In 1998, I was given a new project at Catalent: find a non-animal alternative to gelatin that can be used to make softgels. The project was prompted by the outbreak of bovine spongiform encephalopathy (BSE) and variant Creutzfeldt-Jakob disease (CJD) in the late 1980s and early 1990s. At the time, Catalent was very reliant on gelatin for its softgels, particularly bovine gelatin derived from bone, and there were concerns that the prions that cause BSE could be passed to humans through gelatin. It has since been proven that the gelatin manufacturing process destroys these prions, but at the time it was a big concern in Europe – and there was the potential for future restrictions on gelatin. To be on the safe side, Catalent wanted to find an alternative. Apart from the concerns around BSE, there were also other advantages to replacing gelatin. Gelatin is prone to fluctuations in price and quality – with the quality aspect being particularly worrying for the pharma industry. Indeed, simply changing supplier can mean that you are suddenly working with a completely different gelatin. In addition, gelatin is prone to cross-linking, particularly the high-bloom grades, which can lead to the gelatin becoming insoluble and interfering with a softgel drug's shelf life.

When we were given the project brief, I understood the benefits of replacing gelatin but, at the same time, I remember me and my colleagues staring at one another – we knew it wouldn't be easy. Despite its disadvantages, gelatin is a very versatile polymer with good elastic properties and it usually behaves well in manufacturing. In that sense, it would be hard to beat. Fortunately, we were given a broad canvas to work with and we had the freedom to investigate different production methods, such as radio frequency sealing, reciprocating plates and other forms of encapsulation. We decided, however, that a hermetically sealed envelope using the traditional rotary die process would economically be the best process, which meant that our gelatin alternative would have to possess suitable elastic film strength, as well as being sealable with heat and pressure. We also needed a high solids loading; you can't use high levels of water to form a shell because the capsule will lack strength. We needed to look for polymers that could be typically loaded at 40-50 percent in solution without developing unmanageable process viscosities.

A big challenge was simply the fact that there are a lot of polymers out there to test! Many polymers are excellent gelling agents (too good in some cases). We reviewed all the natural polymers on paper and in the lab, and we did extensive testing of films derived from these natural polymers (using them alone and in combination with each other). I began to look at vegetable-derived alternatives, but many ingredients were excluded on the basis of functionality – often being too poorly elastic, developing high viscosity, requiring high water contents or exhibiting poor film strength. During this time, it really felt as if we'd looked at everything you could think of. As we'd anticipated at the start of the project, finding that perfect gelatin replacement was difficult. Despite the frustrations,

I never thought it would be impossible. I knew that we would eventually find something functional – it was just a case of using the right materials in the right amounts.

A big concern when you work on a cutting-edge project is that the revelation may come too late – what if another softgel company gets there first? You never know what competitors are working on and whether someone will beat you to the finish line. Patents can give you an idea, but they are not published for eighteen months after being filed. (As it turned out, it was actually about another 10 or so years before anyone else came out with a gelatin alternative, so I didn't have anything to worry about after all!)

Starch serendipity

The breakthrough in the project came when a colleague dropped a packet of starch on my desk. He'd been to a trade show and knew about my project, so he brought me a sample just in case it turned out to be useful. The starch was exactly what I needed. On its own, it was ineffective. It formed great films and we could make it seal, but we couldn't process it on our encapsulation machines. By combining it with a polymer (a certain type of carrageenan), we were able to duplicate similar properties to gelatin. We looked at other starches too, from potato, tapioca, and rice, but it was the sample that had landed on my desk that gave the highest loading of solid into a liquid without too much viscosity.

By December 1998, we were making benchtop prototypes and everything was working well. Next, we needed to test the material on the encapsulation machine – it worked and we had our first prototypes manufactured on our pilot encapsulation machine. It was early, rough progress, but we were very proud of our achievement. Our spirits weren't even dampened by a colleague who, when I showed him the prototypes, said, "Do the seals always look that bad?"

In fairness, the capsule seals on the first prototypes were weaker than gelatin seals, which did concern me. However, we managed to address the problem and improve the sealing strength by refining the process, fine tuning the composition ratios and working with suppliers to customize the properties of the raw materials to meet our needs. In addition, there was the shell mass to consider. The gelatin formulations are around 12,000-15,000 centipoise, but our new shell was significantly higher, which meant that we couldn't use traditional gravity delivery into the machine. We tried conventional pumping, but that didn't work either. The main problem was that it needed to be at above 85 °C to form encapsulation ribbons – and the equipment we had wasn't made with that in mind.

Gluing it all together

We eventually sought inspiration from the adhesive equipment industry because viscous glues often need to be delivered at high temperatures using a "melt-

The Medicine Maker Innovation Awards 2016

OptiShell won an award in 2015 - do you have what it takes in 2016? Nominations for the 2016 Innovation Awards are open (http://tmm.txp.to/2016/innovationawards).

We are searching for the most exciting new products of 2016 that are expected to have a substantial impact on future drug development and manufacturing. The winner will have the opportunity to share the story behind their product in a future issue.

For more details, turn to page 3 or email stephanie.sutton@texerepublishing.com.

RP Scherer's Softgels

Modern processes for manufacturing softgels are based on a rotary die encapsulation technique invented by Robert Pauli Scherer in his father's basement in the 1930s. The manufacture is very simple and uses a continuous form/fill/seal process. Two films, or ribbons as they are more commonly known, are used – consisting of gelatin and a plasticizer (the water content is around about 25-40 percent). The ribbons are cast onto cooled drums and then peeled off, lubricated and fed through a set of cylindrical dyes that match the shape of the capsule you require. On top of the dyes, between the ribbons, is a wedge – a metal segment that is heated and has dosing channels that inject the fill material into the forming capsule. In the encapsulation process, the dyes are pressed together with the films to apply pressure to seal the capsule and cut it out of the ribbon. Simultaneously as the seal is forming, the fill material is injected. The capsule then drops out onto a belt and is very soft and pliable at this stage. The capsules are tumble dried, followed by tray drying, and when fully dried become hard. The process is well established, but given that the materials and equipment are quite specialized, softgels are rarely made in house.

Scherer established a company called Gelatin Products Corporation to commercialize the technology, but in 1947 this was renamed R.P. Scherer. Originally, the company focused on nutritional products, but it later became interested in over-the-counter and prescription medicines. Today, R.P. Scherer's technology is owned by Catalent.

on-demand" process – you only melt what you need (the rest remains in the solid form). We took a similar approach with our polymer and since we're only melting perhaps an hour ahead of time, we don't have any degradation issues. Of course, even though the process and equipment were inspired by the adhesives industry, they were obviously engineered to meet higher pharmaceutical standards.

By now, we had the polymer and the process, and everything was very refined. Our global affiliates wanted the product as soon as possible because concerns around BSE were rife, particularly in the UK. Commercial manufacturing and roll out in the UK started quickly – around mid-2000 – and other countries soon followed. The product was called Vegicaps. It was the first natural, GMO free, plant-based shell on the global market. At first, its main use was in nutraceutical and topical cosmetic products.

Finding form for pharma

So where does OptiShell come into this? As soon as the Vegicaps capsules were launched, we went back to the lab to explore the future potential of the shell and how it compared with traditional gelatin softgels. We noticed that the new softgel could be filled at high temperatures. Gelatin softgels can be filled at 37–40 °C before the shell distorts, but our shell was stable up to 70 °C, which opens up the possibility to encapsulate high viscosity liquids and semi-solid formulations, which is a real breakthrough for solubility or bioavailability challenges. In addition, our shell was more resistant to alkaline formulations. We can encapsulate fill formulations with a pH of 12 with excellent stability over three years. Gelatin, on the other hand, is destroyed by acidic or particularly alkaline formulations. Gelatin is also prone to cross-linking, especially in the presence of reactive species such as peroxides and aldehydes; severe cross-linking renders the shell insoluble. Unlike geltain, we found that we could prevent our shell from cross-linking; this is an important feature and means that an OptiShell product will retain the same dissolution characteristics throughout its shelf life.

Finally, the shell is natural. And though this fact doesn't provide benefits in terms of formulation, it is useful from a marketing point of view. I mentioned earlier that the prions responsible for BSE are destroyed in the manufacturing process for gelatin so there isn't a health issue with gelatin. However, since 2000 there has been increasing focus on natural ingredients and non-animal derivatives. Some countries also have rules against gelatin; for example Japan won't allow bovine-derived gels in the country. We've designed OptiShell and chosen the ingredients carefully so that it can be used in all geographic regions. Finally, non-gelatin shells don't have an odor, which is a plus for consumers

Of course, we had to do a lot of work to refine Vegicaps into OptiShell, which is designed to take advantage of all the properties mentioned above. It was a long journey (and I can't give you all the details for obvious reasons) but OptiShell finally launched in 2015. Overall, it is compatible with a wider range of excipients and can be used to encapsulate a range of highly viscous and semi-solid formulations (which facilitates extended release).

Since the launch, OptiShell has already been well adopted by the industry; for example, in June 2016, the FDA approved the first non-gelatin Rx softgel product, which uses a hot fill semi solid matrix in an OptiShell format as its delivery platform. We've seen a lot of interest in the technology, which is exciting for me to witness given that I've been working on the project since the very beginning! I'm looking forward to learning what else lies ahead for the technology.

Keith Tanner is Manager of Technology Development at Catalent and is based in Florida, USA.

Small But Not Forgotten

Is innovation in small-molecule drugs dead? Certainly not – large molecules may grab the bulk of industry headlines, but small-molecule drugs are still pulling their weight. Ongoing research into improving small-molecule manufacturing is just as relevant in the age of biopharma.

In the June issue of The Medicine Maker, we spoke to experts from Ireland's National Institute for Bioprocessing Research and Training (NIBRT). NIBRT focuses on biopharma manufacturing and is involved in a number of ongoing research projects to enhance cell yields and manufacturing efficiencies, but what about small-molecule drugs? There are still many challenges in small-molecule drug manufacture, as well as increasing pressure for companies to use more environmentally friendly chemistries in small-molecule synthesis.

Ireland is not just investing in biopharmaceuticals; the country is also home to the Synthesis and Solid State Pharmaceutical Centre (SSPC), which is based at the University of Limerick. Like NIBRT, SSPC has a focus on drug manufacturing. And although the center also covers biopharmaceuticals, the bulk of its research focuses on small molecules, including synthesis, material isolation and formulation of the final medicine. We speak with Jon O'Halloran, general manager, and Joanne Conroy, industry liaison officer, at SSPC to find out how the center was formed and what small-molecule active drug challenges still plague manufacturers.

What is the story behind SSPC?

Jon O'Halloran: To speak about SSPC, we first have to go back to before SSPC was officially formed. It started with a research collaboration in 2004 between the University of Limerick and a local company that produces alumina from bauxite ore. It is located very close to the University of Limerick, which is where SSPC is hosted today. The company wanted to continuously produce aluminum from bauxite ore in the most efficient, cost-effective manner possible, so they approached a couple of researchers from the university: Kieran Hodnett whose background lies in physical property science, and Patrick Frawley, who specializes in modeling. The project was successful – the team managed to obtain European funding and redesign the alumina refining process. Today, the plant is one of the most efficient in the world at producing alumina – and it was a very important development for the site, which at the time was under a lot of cost pressures. It continues to thrive to this day.

After the completion of the project, Mary Shire who worked in the university's technology transfer office – and had previously worked in the pharma industry – was inspired. After seeing the success with alumina process

Jon O'Halloran

Joanne Conroy

(which involves the crystallization of fine chemicals), she realized there were similar chemistry challenges in the pharmaceutical industry, such as the crystallization of active pharmaceutical ingredients (APIs). Perhaps the researchers' work on the fundamentals of crystallization could be put to even greater use.

The researchers, together with Hodnett (who is the scientific director of SSPC today) and Shire, approached the pharma industry, via their trade association, Pharma Chemical Ireland. The idea was pitched to 10 companies, who liked what they heard. Hodnett then began reaching out to other academics in the space, including Brian Glennon at University College Dublin, who specializes in pharmaceutical engineering; Anita Maguire (organic chemistry) at University College Cork; Pat McArdle (analytical science) at the National University of Ireland; and Anne-Marie Healy (pharmaceutics and pharmaceutical technology) at Trinity College Dublin's School of Pharmacy and Pharmaceutical Sciences. Once the team was together, things began to take shape. The pharma companies engaged with the research team and the research office of the University of Limerick, and funding of almost 7 million Euros was sourced from Science Foundation Ireland (SFI) for 2008 to 2012 to create a Solid State Pharmaceutical Cluster.

During this time, the cluster concentrated on helping companies to demystify the black box of pharmaceutical crystallization. It was a huge success – to the point where Irish manufacturing affiliates of multinational pharma companies were now exporting crystallization solutions to their sister manufacturing sites overseas. Prior to SSPC, these sites would have been exporting problems to corporate R&D in this space. The industry in Ireland had come a long way in just 4 and a half years of SSPC.

By 2012, we were at the end of our funding and we asked our pharma partners what they thought should happen next. In the end, we were able to obtain further funding through SFI – and from the pharma companies themselves – to the tune of over 40 million Euros, which will last until 2019. The Synthesis and SSPC was formally launched at this time and its activities go beyond crystallization. We look at upstream chemistry and downstream formulation activities, as well as having activity in the biopharmaceuticals space. We have 24 industry partners and we've expanded the number of research institutes that we work with to nine, which includes NIBRT.

I think our greatest achievement to date has been facilitating multi-partner (both academia and industry) collaboration in the precompetitive space. Traditionally, problems would be solved in house, or perhaps companies would work with just one academic partner. This is one of the first times that multiple companies and research partners have come together to solve pharmaceutical manufacturing challenges.

How did you get involved with SSPC?

JOH: I've spent 20 years in the pharma industry, predominately in API manufacturing roles. I started out as a process development chemist, but later I moved into manufacturing and on to senior management roles in production and business development. I had wanted to further my career and education – and in 2008 the SSPC role was advertised and was ideal for both. I was also attracted by the research question that SSPC wanted to address. In my time in industry, I felt

that some of the problems we were trying to solve weren't best understood with the knowledge we had. I was very keen to understand more about the fundamentals of crystallization.

Joanne Conroy: I'm quite new to SSPC – I've only been here for four months – but I have worked in the pharma industry for 10 years as an organic chemist. I started my career in medicinal chemistry working for Novartis in Basel, but I've spent most of my time in the industry at the later stage of drug development in product development with GlaxoSmithKline's second generation team. I also worked for a number of years in manufacturing at GSK's Cork site in Ireland. Today, I'm the industry liaison officer at SSPC. It's very different to working in the industry and it's taken me a while to stop saying "we" as in "we at GSK"! I'm still very much connected with the industry though – we need to make sure they have a steer on our projects to ensure that our work is relevant.

Biopharma grabs most of the industry's limelight – are small molecules overlooked?

JOH: Biopharmaceuticals are certainly the emerging and growth area within the sector, and certainly significant when it comes to sales. However sales are determined by price, as well as unit volume, and biopharmaceuticals are quite expensive. Manufacturing a large molecule product is generally more complicated and expensive than manufacturing a small molecule product. Both are very important however – and will continue to be so going forward, with most companies estimating an even distribution of small and large molecules in the future.

Looking at small-molecule APIs, in all honesty I don't think that the sector has changed to the same degree as most others in the past 50 years. We are still talking about tablets and capsules (and will continue to do so in the future) and most companies still manufacture in batch mode. If you look at any other sector globally, you'll see that most process industries manufacture continuously. The pharma industry has been very slow to get moving in this area, although serious initiatives around continuous manufacturing are now starting to be realized; SSPC is very active in this drive.

Irish Talent and Innovation

According to Joanne Conroy, Ireland is the eighth largest producer and the fifth largest exporter of pharmaceuticals globally. In addition, 9 of the top 10 pharma companies have a presence in Ireland. If you're interested in the Irish pharma industry, you can read more on The Medicine Maker website:

Sustaining the Biopharma Boom, by Killian O'Driscoll, NIBRT, http://bit.ly/2b37C2m

Finger on the Biopharma Pulse, with John Milne, NIBRT, http://bit.ly/2axat4a

Know Your Process, Know Your Product, by Jonathan Bones, NIBRT, http://bit.ly/2aIHhWr

Believe in Bioinformatics, with Colin Clarke, NIBRT, http://bit.ly/2aIRiSi

A Tale of Irish Biopharma, by Barry Heavey, IDA, http://bit.ly/2aIQGfi

I believe there is a sea of change coming. We have all heard of the "patent cliff" and we know that there are smaller numbers of blockbuster drugs. There is also a shift towards more niche products, particularly high potency, lower dosage small molecules, which create new challenges in terms of manufacturing as many small-molecule drug manufacturing operations are built to produce a large tonnage of API.

JC: Both novel technology and novel chemistry are needed to manufacture APIs more cost effectively. Many innovator small-molecule drug manufacturers must compete with generics. The patents on many innovator drugs have expired, but many patients are still prescribed the branded product. To ensure that this continues to happen, innovator companies need to make sure their drugs are cost effective. And costs can be reduced through chemistry.

In particular, green chemistry is seeing a lot of attention as companies look to reduce their carbon footprint (many have very aggressive targets in mind). Biocatalysis is one way to achieve this since it involves carrying out mild reactions using an enzyme as a catalyst. A lot of these reactions can be carried out in water, which eliminates the use of toxic and highly flammable solvents.

A significant number of APIs are single enantiomers and many of the synthetic routes to these drug substances will involve a chiral resolution, which is extremely wasteful as the undesired enantiomer is an unwanted byproduct that has to be removed. If the chemistry can be designed so that you make the desired enantiomer from first intent, either using an enzyme or another asymmetric catalyst, then you can create a much greener and more atom efficient process. Another area of interest in designing organic synthesis is C-H activation reactions. Most organic chemistry reactions involve new carbon-carbon bond-forming reactions; there is a lot of work being done to ensure this process is efficient.

How does SSPC work with NIBRT?

JOH: Around 90 percent of our research is in small molecules, but many of the companies we work with deal with both small and large molecules – and they don't want us to forget about the large molecules. Recently, we've been working with NIBRT in the area of disposable technologies. Disposable, single-use systems have been a real conundrum for the industry in terms of extractables and leachables, and how these can affect large molecules. With industry and in collaboration with NIBRT, we have funded a project through SFI with a view to determining the properties of disposable technologies that are most critical. We hope to engage in further research with NIBRT in the future too.

What research have you been focusing on at SSPC?

JOH: Outside of our biopharma research, we have three strands of research. Strand 1 focuses on research concerning the making of the molecule, such as chemistry, biocatalysts, green chemistry, telescoping reactions and so on. Strand 2 looks at producing materials, with a focus on crystal growth and design, and Strand 3 looks at drug product formulation and manufacture. Looking at the trends in Strands 2 and 3, solubility is a big issue. There is a common statement used in the industry: for every one drug that makes it to market, 10,000 fail. One of the reasons for these failures is poor solubility. A lot of the work we do in Strands 2 and 3 aims to help poorly soluble compounds become more promising. We do a lot of work with nanoscale materials; if you can make materials of a sufficient nano scale they can be much more soluble and as a result lead to greater bioavailability. However, it is challenging to retain the nanoscale through manufacturing. We also work to realize the medicines of the future, such as multicomponent systems and cocrystals. In the area of drug delivery, we look at how to deliver poorly soluble drugs by use of techniques like spray drying and hot-melt extrusion.

JC: In strand 1, we are doing some very interesting work on flow chemistry and

continuous manufacturing – this is a topic (and a challenge) that brings a lot of companies together. Replacing traditional batch conditions with flow chemistry allows synthetic routes that would have previously been rejected by pharmaceutical manufacturers due to safety and operability concerns to now be revisited. Companies are looking for continuous platforms – and they have been leaning on SSPC in this area. I don't think the plant of the future will be using 10,000 liter vessels; manufacture is more likely to depend on a process that can take place at lab scale – perhaps producing tens of kilos per hour or day. This can satisfy the market where dosages are quite small and potencies high.

"We also work to realize the medicines of the future, such as multicomponent systems and cocrystals."

How keen is the industry to embrace continuous manufacturing?

JOH: In an industry that is traditionally seen as conservative, there can be a resistance in pharma in being the first to do something new, especially when novel manufacturing techniques can be viewed as disruptive. It can also be expensive to go it alone with potentially high-risk novel new processes. Now that some companies have switched to continuous, more are following. Vertex in the US was the first to have a continuous process approved for a new drug in July 2015, and since then there have been developments at other companies. In April, Janssen made the switch from batch to continuous for an already marketed drug, which was a big step. But these developments mostly revolve around the drug product.

In terms of the API, SSPC and companies are working to advance the area of flow chemistry, but there are quite a few knowledge gaps in the API workup space and we're receiving a lot of interest in terms of continuous crystallization and drying. We recently received a 2.4 million Euro grant from SFI to build a testbed in this area for industry and researchers to develop together.

There are also regulatory challenges for the sector in the area of adoption of continuous processing. Next year, we're organizing a continuous manufacturing workshop in Dublin with the FDA and EMA to discuss the challenges associated with implementing continuous manufacturing in more detail.

Overall, I'm very positive about the area. Slowly, the conversations are moving and there is a realization that it's not a question of "if", but "when" the pharma industry will move to continuous. However, I'd like to see the industry be more open to change. There are a lot of promising advances on the horizon; for example, we are all hearing about stratified and personalized medicines, convergence with medical devices , and treating the societal needs of the future with ageing populations and ambient assisted living. The sector needs to be open to change and, indeed, embrace it. The time is ripe for disruptive technologies and new processes – and at SSPC it is exciting to be helping to deliver that change.

Raising Standards

Sitting Down With… Susanne Keitel,
Director of the European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe in Strasbourg, France.

Did you ever expect to have such a prominent position in pharmaceutical standards?

No, it never crossed my mind. Thinking about it, I really don't know what I wanted to be as a child. I was very interested in science from a young age, so I think it was clear early on that I would do something related to natural sciences. I decided to study pharmacy as it allowed me to cover a broad combination of topics from chemistry to biology to physics, as well as the more "medical" disciplines, such as pharmacology and toxicology. After school, I worked in a community pharmacy. This gave me insights into the man-on-the-street's perspectives and concerns.

What happened after you graduated?

After graduating, I decided to pursue a PhD in pharmaceutics. My focus then was on research. It was only later that the important place regulation has in the development and quality assurance of medicines became clear. At that time, I was working in pharmaceutical development at a research-based, globally active pharmaceutical company in Berlin. I worked there for 10 years. During this period, I was involved in a lot of international projects and developed a significant insight into regulations and standards in Europe, Japan and the United States, as well as issues related to their harmonization.

How did you make the switch to the other side?

I saw a vacancy notice for a senior position at BfArM, the German licensing authority (the Federal Institute for Drugs and Medical Devices) and I decided that it would be very interesting to put the experience I had gained in the pharma industry to new use. In the US, regulators and people in industry frequently swap sides, but this is less common in Europe – people tend to pick a side and stick with it. Personally, I think it's very important for a regulator to understand how decisions impact the industry they regulate – and direct experience is hard to beat in that regard.

At BfArM, I was first responsible for the assessment of the quality part of applications. In addition, I was chair of the German Pharmacopoeia Commission. Later on, I took on additional assignments such as managing European licensing procedures with BfArM involvement. Finally, I was responsible for the executive department of European and International Affairs. Throughout my 10 years at BfArM, I represented Germany in different working groups and committees of the European Medicines Agency and the European Commission. Until moving to the Council of Europe in 2007, I also represented the EU in quality related expert working groups at the International Conference on Harmonization. I have always considered participation in inter-disciplinary and international expert groups as one of the highlights of my work, and for me it was a natural continuation to take up my position as director of the EDQM in 2007.

You've recently been busy launching the latest edition of the European Pharmacopoeia...

The 9th edition of the European Pharmacopoeia was released recently and the standards will come into effect on January 1, 2017. More than 50 percent of the 9th edition contains new and revised text compared to the previous edition. This new edition is also much larger than its predecessor and now has three volumes as opposed to the previous two. It also covers new emerging fields, such as aspects related to cell and gene therapy products. Our aim is to provide manufacturers not only with legal standards, but also with information and support. It is very satisfying to see how the European Pharmacopoeia has developed and expanded to continue meeting the needs of its stakeholders.

What do you consider to be today's biggest industry challenges?

Right now, I think the most important challenges facing the industry are the cost pressures in the public healthcare systems. Companies are under enormous pressure to lower prices, whilst also having to deal with increasing competition from China and India. Of course, we as regulators are also under economic pressure – the EDQM is part of the Council of Europe and our member states have been economically stronger in the past. The European Pharmacopoeia also relies on the support of more than 700 experts nominated by the 37 member states and, for example, frequent mergers in the pharma industry impact our pool of experts because they tend to lead to R&D site closures – reducing the number of scientists in R&D and therefore the availability of industry experts.

What do you enjoy most about your role?

Working for the EDQM is tremendously rewarding because our efforts clearly make a difference. The EDQM demonstrates the benefits of collaboration and work-sharing. Member states working with us can achieve much more together than working in isolation – something that is really satisfying, and yes, includes an element of pride for what we do. Our work at EDQM facilitates access to quality medicines. We are also involved in other areas, such as fighting falsification of medical products, developing guidance for organ, tissue and cell transplantations as well as blood transfusions, just to mention a few.

The role as head of EDQM has many challenges, all working toward providing the best support for protecting public health – of course for member states, but also beyond. In this context, it is very rewarding for me to be able to rely on a very competent and committed team at the EDQM and an excellent network of international experts.

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