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Pharma Braces Itself for Post-Brexit Regulatory Changes

The repercussions of EMA’s relocation and Brexit will continue to be the dominant regulatory issue throughout 2018.

The European pharmaceutical industry is hoping that 2018 will be a year when a number of regulatory uncertainties will at least start to be resolved. The biggest of these issues are the regulatory reverberations of Brexit, in particular, the impact on the regulatory work of the London-based European Medicines Agency (EMA) having to move, as a result of the United Kingdom’s withdrawal from the European Union, to new offices in Amsterdam.

The relocation of EMA to Amsterdam

There have already been doubts about the speed of implementation of some key pieces of approved EU legislation. Now there could be further delays to the enforcement of new laws because of the possible disruption of the transfer of EMA’s headquarters. In addition, the agency, which handles the centralized approval of new drugs and variations to their authorizations while also coordinating the regulatory activities of the EU’s 28 member states, is also drawing up new guidelines for existing legislation.

Brexit is due to take place at the end of March 2019. But its regulatory effects will start to hit companies from early 2018, particularly those based in the UK or with subsidiaries in the country. After Brexit, the UK will become a non-EU state classified as a “third country” in EU legislation with a legal position in relation to Union rules much the same as other countries outside Europe. The country is likely to assume its new legal status only after the end of a transition period of at least two years starting in April 2019. The availability of a transition period is considered by the industry to be particularly important. “[We and other industry] organizations are of the opinion that the agreement of transitional arrangements after March 2019 will be critical in ensuring there is minimal disruption to patients receiving medicines after the UK leaves the EU,” a spokesperson for the European Federation of Pharmaceutical Industries and Associations (EFPIA) told Pharmaceutical Technology Europe.

Public health and economic consequences

The extent of Brexit’s repercussions on the pharmaceutical and related industries, both in the UK and the remaining EU member states, will depend on the final deal reached in the current UK–EU negotiations on withdrawal and whether a free trade agreement (FTA) is included. A deal is due to be achieved by October 2018 to give the European Parliament and the 27 member states time to approve it. One outcome could be that the UK and its licensing agency, the Medicines and Healthcare products Regulatory Authority (MHRA), will continue to be involved in the EU’s medicine approval and other public health activities in much the same way at present.

Under this scenario, Brexit’s public health and economic consequences would be “minimal” for both the EU and the UK, according to a report (1) on the public health implications of Brexit, completed in November 2017 by the London-based Office of Health Economics (OHE), a consultancy partly funded by the pharmaceutical industry.

Two other scenarios described by OHE would involve the UK introducing a standalone regulatory system within the context of a UK–EU free trade agreement. In the absence of a free trade agreement, trading between the two would be conducted under the rules of the World Trade Organization (WTO). With both outcomes, there would be mutual recognition agreements (MRA) on good manufacturing practice (GMP) and other regulatory inspections but not of batch release processes.

In the OHE’s worst-case scenario, the UK–EU negotiations would breakdown without a deal on public health cooperation or MRAs. Trade between the two would be controlled entirely by WTO rules.

Amidst a lack of legal certitude, UK-based companies and business are having to plan for the possible transfer of market authorizations to legal entities in the EU’s remaining 27 member states or for the application for new authorizations, which would be among a number of additional burdens on EMA before and after Brexit.

Pressure on EMA activities

The agency has been given 16 months to complete the move of its headquarters to Amsterdam, which was selected as the new base on 20 Nov. 2017 by the EU member states out of submissions by 19 cities across the Union (2). Pharmaceutical companies are concerned that the 16-month period will put extra pressure on EMA’s activities, which because of Brexit complications, could be disrupted well beyond 2019.

“The real work starts now,” said Beata Stepniewska, deputy director general and head of regulatory affairs at Medicines for Europe, representing generic drugs and biosimilars producers. “Looking to the next steps in the process, we hope that the relocation plan will be comprehensive and implemented effectively, which will provide certainty for both EMA staff and for the continuity of the work of the agency,” she told Pharmaceutical Technology Europe.
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Approximately 200 of EMA’s 900 staff in London have indicated they will not be staying with the agency after the transfer. Some of these staff could have expertise that may turn out to be difficult to replace. Another problem is that the agency’s new offices in Amsterdam will not be ready for full occupation until 2020. In the meantime, some of EMA’s work will have to be done from temporary premises elsewhere in the Dutch city.

“A major concern is the uncertainty about not having a building that is ready [for full occupation],” Guido Rasi, EMA’s executive director, told a press briefing in London in November 2017 after the selection of Amsterdam for the new headquarters. “The loss of staff will not cause delays in approvals of new medicines but possibly delays in other services,” he continued. “The main challenge is not going to be the physical relocation but [assuring the continuity] of activities for the benefit of all the citizens of Europe.”

Impact on other medicines agencies in Europe

Among Europe’s medicines agencies, it will not just be EMA and the UK’s MHRA that will be working hard in 2018 to prepare for the post-Brexit regulatory changes. Agencies in the EU’s 27 remaining states and in the three non-EU countries—Norway, Iceland, and Leichtenstein—in the European Economic Area (EEA), which are also in the EU’s pharmaceuticals single market, will be taking on more regulatory, monitoring, and testing responsibilities. This will particularly be the case for regulators outside the UK if the country has to opt for a standalone regulatory status.

After being headquartered in London since its foundation in 1995, the MHRA had been taking on a disproportionate amount of rapporteur work on the assessment by EMA committees of new medicines under the centralized approval system. Now assessment tasks are being shared out more equally among specialists in the agencies of EU member states. Also, authorizations handled by the MHRA under the decentralized mutual recognition will have to be transferred to national agencies.

In addition to approximately 1000 licences granted under the EMA-based centralized system, approximately 5800 national market authorizations are held by UK-based legal entities, according to figures from EFPIA. “Where marketing authorizations holders (MAH) are based in the UK, these would need to be transferred or duplicated to an MAH in the EU27/EEA,” warns the OHE in its report (1). “The same applies for MAHs based in the EU27/EEA being transferred or duplicated in the UK.”

Supply chains and post-authorization monitoring

The UK pharmaceutical, chemical, and biotechnology sectors play a big role in intra-EU pharmaceutical supply chains in the production of starting materials and intermediates through to finished products. These supply chains are starting to be reorganized to reduce the role of UK-based producers with pharmacists in the country already reporting medicines shortages which will inevitably worsen over the next year and into 2019. The UK not only has the EU’s second highest number of GMP and other medicinal manufacturing sites but the third highest number of batch certification sites. Replacement batch release sites in the EU/EEA will have to be set up with qualified personnel. “The impact of no mutual recognition of batch release would be substantial for the EU27/EEA and the UK,” says the OHE (1).

Alterations are also likely to be needed in the monitoring of the quality, safety, and efficacy of medicines in the post-authorization stages. The UK contains the EU’s highest number of centres for conducting pharmaco-epidemiological studies. Mainly because of the centralized nature of its National Health Service, it also conducts the highest number of post-authorization safety studies (PASS), according to the OHE report (1).

Preparing for serialization

Meanwhile, even if there was no Brexit, pharmaceutical companies would have to reorganize some of their activities in 2018 in order to prepare for the implementation of new EU legislation. A major task is ensuring compliance, by March 2019, with part of the 2011 Falsified Medicines Directive (FMD), which requires the serialization or unique identification of each medicine pack, necessitating major changes to packaging lines and distribution channels.

“It is a very complex process including regulatory readiness to implement the safety features on packaging,” says Stepniewska. “In view of the huge amount of packages that are affected, a lot of notifications to the competent authorities are expected to be submitted already in 2018, which will create a serious challenge for the pharmaceutical regulatory system, besides Brexit.”

EMA has indicated that the implementation of the 2014 Clinical Trials Regulation, which includes new rules on the quality of investigational medicinal products, may be delayed further after being put back to the second half of 2019. Similarly, the European Commission, the EU’s Brussels-based executive, may hold back the introduction of a new strategy on Pharmaceuticals in the Environment (PIE). In a year of pre-occupation with Brexit-induced legal uncertainties, these delays may not be unwelcome among both regulators and many pharmaceutical companies.

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Drug Pricing and Quality Are Top Issues for the US in 2018

Policy makers in the United States look to boost generic drugs, curb opioid abuse, and maintain incentives for innovation.

Concerns that high and rising drug prices hinder patient treatment will continue to shape pharmaceutical markets in what promises to be a tumultuous year in Washington, DC. Policy makers will weigh access to medicines with the desire to encourage biopharmaceutical R&D, which relies on regulatory efforts to streamline clinical research, ensure product quality, and achieve more efficient oversight. The November mid-term Congressional elections already are heating up, as Republicans seek to maintain control of the House and Senate amidst continuing debate over government funding and healthcare policies. These developments will affect resources and initiatives for the US Food and Drug Administration, the US National Institutes of Health, and US federal and state health programmes.

Global regulatory issues will be important, as drug sourcing and production expands overseas and disease outbreaks threaten public health around the world. International harmonization of regulatory standards and mutual recognition agreements will advance as authorities look for efficiencies in ensuring drug quality, in managing product lifecycles, and in blocking illegal trafficking of counterfeit drugs. Drugmakers also face extensive changes under Brexit, including relocation of the European Medicines Agency to Amsterdam and the need to ensure appropriate marketing authorizations in Europe.

Coverage and controls

The heated, ongoing debate over revising the Affordable Care Act (ACA) and state Medicaid and children’s health programmes in the United States will remain in the spotlight as manufacturers evaluate how policy changes may limit drug coverage and reimbursement. Pharma companies backed the ACA and agreed to pay millions in additional taxes to expand pharmacy benefits. Now consumers may face higher out-of-pocket costs that will squeeze drug utilization and ignite further efforts to reign in pharmaceutical prices. The US Centers for Medicare and Medicaid Services (CMS) recently revised how Medicare Part B pays hospitals for administering certain drugs and seeks to facilitate coverage of newly approved biosimilars and generic drugs. A new proposal calls for Medicare Part D prescription drug plans to share with patients the rebates and discounts negotiated by manufacturers and pharmacy benefit managers (PBMs). This push for more transparency in drug prices and discounts could erode revenues for PBMs and further escalate the finger-pointing by manufacturers, insurers, and PBMs over who’s to blame for high-priced medicines.

These trends will build interest in value-based pricing strategies that link drug reimbursement to patient response to treatment. CMS and insurers also contemplate arrangements that spread reimbursement over several years for important one-time therapies. Manufacturers will need strong data to justify launch prices, especially for targeted therapies. And payers will look more to reports from the Institute for Clinical and Economic Review (ICER) and other third-party analysts on whether benefits of a new medicine justify costs.

FDA wants manufacturers to update facilities and processes to ensure more reliable production.

Encouraging innovation

A main concern for the biomedical research community is that any form of price controls would discourage private investment in biomedical innovation and limit development of new cures for critical diseases. Even though drug companies enjoy healthy profits, policy makers are reluctant to dampen the current boom in scientific discovery that has led to new gene and cellular therapies and robust R&D pipelines. FDA approved more than 40 novel medicines through early December 2017, heading for a record year.

US-patent policy and market exclusivity provisions are crucial to maintaining an inviting climate for investing in the biotech industry, but issues have emerged about innovator firms using patents to block competition. The development and marketing of new biosimilars face delays from intense patent battles, and a recent effort to extend protections by transferring patents to a Native American tribe has generated a strong backlash. These actions fuel questions about overextended exclusivity periods for newly approved drugs and biologics, particularly for orphan drugs and reformulated products. The US Supreme Court will weigh related issues as it considers an important case in 2018 that could revise the current US Patent Office process for reviewing patent challenges.

While FDA generally avoids involvement in pricing issues, commissioner Scott Gottlieb looks to enhance consumer access to medicines by promoting market competition. A main strategy is to speed the development and approval of generic drugs, particularly for complex therapies and combination products
and in classes dominated by one or two brands. Gottlieb also wants to prevent brands from blocking generic-drug makers from obtaining supplies needed for bioequivalence testing and other tactics that delay market entry.

More efficient and timely FDA review and approval of new medical products also will enhance competition, and the agency should gain added flexibility in this area from implementing the 21st Century Cures Act and reauthorized user fee programmes. Further advances should emerge in the coming months as Gottlieb unveils more proposals for spurring efficient clinical research methods, particularly to broaden indications for cancer therapies, and wider use of digital technology and updated information systems. Janet Woodcock, director of FDA’s Center for Drug Evaluation and Research (CDER), is working to further automate and better manage the technology and updated information systems.

To meet goals for the timely evaluation of applications for these cutting-edge medicines, including priority generics, FDA wants manufacturers to update facilities and processes to ensure more reliable production of high-quality medicines so that manufacturing issues will not delay the approval of new breakthrough drugs or biosimilars. To this end, FDA is requiring applications for new drugs, biologics, and generics to list all facilities involved in product testing and production in order to meet accelerated review goals. Ongoing shortages in sterile injectibles, biotech therapies, and even conventional drugs spotlight the need for industry to invest in modern facilities and quality operations able to detect and prevent distribution of adulterated and contaminated medicines.

**Combating opioids**

The deadly opioid epidemic, which is taking thousands of lives and driving up healthcare costs on every level, presents serious challenges to pharmaceutical companies. Health authorities and medical practitioners recognize the need for pain medicines for patients with genuine need of treatment, while also struggling to curb excessive prescribing and distribution of drugs subject to abuse and misuse. Congress and the White House have rolled out policies and plans for limiting inappropriate opioid use and for expanding treatment for addicts and access to opioid overdose rescue drugs to lower the death rate from abuse and will look to implement new strategies more effectively.

FDA has ramped up its direct involvement in tackling opioid abuse by encouraging research on new non-opioid pain treatments and more effective medicines to prevent and treat addiction. A related goal is to help overcome hurdles in developing low-cost generic abuse deterrent formulations (ADF) and overdose treatments and to devise more secure packaging and distribution strategies for pain medications.

On the international front, FDA is collaborating with other agencies to combat import of falsified/substandard medicines, including dangerous pain treatments from overseas. At home, opioid manufacturers face criminal investigations and lawsuits for excessive marketing and distribution of these products, including dangerous pain treatments from overseas. At home, opioid manufacturers face criminal investigations and lawsuits for excessive marketing and distribution of these products, and legal challenges are likely to escalate as overdose rates continue to rise.

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What to Watch for in 2018

The industry will see an impact from financing, M&As, advanced therapies, generic drugs, and the retail market in the new year.

It was a great year for much of the bio/pharmaceutical contract manufacturing and development (CDMO) industry in 2017. Research organizations continued to generate hundreds of new candidates, while venture capitalists and private equity investors maintained a robust flow of new funding to emerging bio/pharma companies, which are highly dependent on CDMOs. An active deal environment provided rich exits for CDMO founders and investors.

The momentum from 2017 looks like it will continue into 2018, but one should never extrapolate today’s trends inexorably into the future. Here are five industry themes to watch closely for their potential impact on the CDMO industry.

Bio/pharma financing

The demand for CDMO services has historically been tied to funding cycles for emerging bio/pharma companies, and 2017 was the fifth year of the upward slope of the funding cycle that began in 2013. The capital raised by emerging bio/pharma in 2017 should certainly maintain demand for CDMO services through 2018. Indeed, new business bookings by clinical contract research organizations (CROs), a bellwether for development activity, remained quite strong through 2017.

CDMO executives should keep a close eye on the fundraising environment, however, especially the public equity markets. Availability of capital can be impacted by factors external to the industry that change investor psychology, even when underlying industry fundamentals are unchanged. Those factors include a general economic slowdown (which many economists are predicting for 2019), rising interest rates (a reality), and political uncertainty (2018 is an election year in the United States). On average, emerging bio/pharma companies have only 12–15 months of cash on hand, and they are likely to slow their spending at the first sign that raising new capital could be difficult.

Mergers and acquisitions

There were some very large deals in the CDMO industry in 2017, and a lot of smaller ones. Private equity firms continue to be drawn by the high level of drug development activity and the opportunity to roll up small CDMOs into larger entities. Larger CDMOs continue to pursue strategic acquisitions that add technical capabilities and provide entry into new market segments.

The momentum from 2017 looks like it will continue into 2018, but one should never extrapolate today’s trends inexorably into the future.

The industry will see more M&A activity in 2018, but the pace may slow down. Valuations have gotten quite high, even for smaller properties that require investors to fund substantial additional capital for capacity expansions and upgrades. Financing will get progressively more expensive as interest rates rise during the year; that could force valuations down but potential sellers may balk at taking lower valuations than their competitors got just a few months ago.

One development to watch for is a very big deal involving an industry leader, along the lines of Thermo Fisher’s acquisition of Patheon and Lonza’s acquisition of Capsugel in 2017. The largest CDMOs need to do deals to deliver on promises to investors and to increase their ability to service global bio/pharma companies with their billions in manufacturing and R&D expenditures. It would not be surprising to see another large private equity firm or strategic buyer from outside the industry make a game-changing entry into the CDMO industry.

Advanced therapies

New treatment modalities such as gene therapy, cell therapy, and antibody drug conjugates are becoming a bigger part of the new drug pipeline. Most of the candidates are early stage, with a high
Outsourcing Review

percentage still owned by academic institutions, but some initial clinical successes in actually curing once-incurable diseases is stoking investor interest, and established bio/pharma companies are actively buying up advanced-therapy companies.

Advanced therapies present a challenge for CDMOs because their business model and technology often don’t fit the traditional CDMO model. Many of the candidates are autologous (i.e., they involve taking cells from a patient, processing them with the sponsor’s technology, and re-injecting them into the same patient). That is very different from the CDMO model of producing multiple units of a single product.

Still, a number of entrepreneurial CDMOs have positioned themselves for advanced therapies, and several established CDMOs have built positions that are expanding with acquisitions and internal investment. Demand for these services appears strong, and the industry can expect to see further M&A activity in this sector during the year, as major CDMOs look to add advanced therapies to their portfolios.

Restructuring in generic-drug industry
Pricing and margins for generic drugs continue to spiral downward, and regulators and payers are determined to keep the pressure on. In the US, the US Food and Drug Administration commissioner has promised new procedures and regulations to speed approval of generic drugs, and the nominee to head the Department of Health and Human Services has promised to focus on bringing drug prices down. In Europe, the turn from branded to commodity generics has undermined the industry’s profitability as governments use tendering to purchase pharmaceuticals.

The pressure on generics has significant implications for the bio/pharma CMO industry. Much of the industry has been dependent on branded generics, especially the European CMOs. Lost volumes and narrowed margins, compounded by overcapacity in solid dose manufacturing, are forcing CMOs to restructure, including facility shutdowns.

The problem could be compounded by the restructuring efforts of the large generic-drug companies themselves. Some, like Teva, are committed to downsizing their sprawling and inefficient manufacturing networks. Others, like Sandoz, are reportedly preparing to exit the solid dose portion of their business, which is also likely to result in plant closings. The risk to CMOs is that some of the closed or divested manufacturing facilities will end up becoming CMO operations themselves, worsening the overcapacity problem.

Retail revolution
CMOs will do well to follow developments in the retail supply chain, because they could create new opportunities and challenges. The pharmaceutical industry was rocked at the end of 2017 when the retail and mail order pharmacy giant CVS announced that it intended to buy health insurer Aetna. If the deal were to go through, it could drive a lot of changes in the healthcare delivery system, concentrating more market power in the hands of a few large integrated providers.

Pricing and margins for generic drugs continue to spiral downward, and regulators and payers are determined to keep the pressure on.

The CVS–Aetna announcement came in the midst of speculation that Amazon is preparing to enter the drug distribution business. The online retailing giant threatens to disrupt the way patients get their drugs today thanks to its large customer base, skill in app-based ordering, warehousing and distribution scale, and willingness to take low profit margins.

The kind of market power that might be accumulated by CVS/Aetna and Amazon could create new demands on drug sponsors and manufacturers over issues such as price, inventory maintenance, just-in-time delivery, and packaging. CMO executives should probably devote some time to understanding the implications of those downstream changes and begin thinking about how they should respond. PTE

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Pharmaceutical Technology Europe JANUARY 2018 13
As real game-changers in the treatment of diseases, biologics have a dominant share in the global pharmaceutical market today. EvaluatePharma has projected that by 2022, biologics will make up 52% of the top 100 product sales, overtaking small-molecule drugs (1). It is, therefore, not surprising that biologics are becoming a major part of drug development pipelines, especially for Big Pharma. The number of new biologics on the market has been growing steadily despite the highly complex production process; however, because of delivery challenges associated with non-invasive routes, most of these drugs will be developed for parenteral administration.

The focus of product development has evolved into making parenteral administration more convenient for the patient or healthcare provider while improving manufacturing, notes Martin VanTrieste, an expert and consultant in all aspects of quality in the pharmaceutical industry, who previously served as senior vice-president at Amgen, responsible for quality assurance, quality control, compliance, and operational excellence. “Packaging has thus become an integral part of the drug concept,” he says. “Besides contributing to patient safety, parenteral packaging should also allow for more flexibility, such as the use of different filling lines. It should facilitate manufacturing and contribute to a lower total cost of ownership, which can be achieved through standardization, for example.”

Pharma manufacturers are generally looking for smooth and reliable processes, observes Markus Hörsch, sales and marketing director at Bausch + Stroebel. “Due to increasing drug costs and the associated rise of unit value, pharma manufacturers are seeking to minimize product loss during the filling operation. There is a lot of interest in all kinds of process controls. We notice that such applications are being requested more and more to prevent rejects and raise process safety,” he says.

Packaging solutions shaped by industry trends

The challenges of parenteral packaging facing R&D-driven pharma companies arise from three significant trends shaping drug development and manufacturing activities. Firstly, the shift toward customized therapies that target smaller patient populations is driving the demand for more efficient and flexible fill/finish processing, VanTrieste observes. Smaller batches require small, flexible fillers, which are able to process multiple containers such as vials, syringes, and cartridges, Hörsch points out. “Pharma manufacturers want the flexibility to process different products and containers on the same machine and at the same time, while minimizing changeover times. Fast changeovers between different packaging containers are, therefore, important,” he explains. “Today, more and more containers as well as the components are supplied as ready to use, which means they are already washed and sterilized. Thanks to such formats, pharma manufacturers can focus on their core business of filling their product.” VanTrieste, however, adds that there is a need for standardization of ready-to-use packaging platforms.

Secondly, there is an increasing number of highly concentrated, and thus, highly viscous drug formulations, which require high-dosage accuracy. “Extremely accurate container volume specifications (such as inner diameter and length) are needed..."
for such formulations,” VanTrieste explains. Thirdly, the trend toward higher dosage volumes with longer administration times is triggering the need for device integration to enable convenient self-administration outside the hospital setting. “In this case, accurate dimensions for enhanced container/device compatibility are required,” VanTrieste says.

“Taking all these requirements into account and considering the huge number of already marketed therapies and existing drug/packaging configurations, it becomes evident that future pharma packaging has to be a modular concept,” VanTrieste highlights. “Thus, the most important question is: what is the most sufficient packaging solution per therapy, determined by patient, drug, and fill/finish requirements.”

**Early collaboration is crucial**
The risks associated with packaging are often not at the forefront of early stage development, but for biologics particularly, the container can have a profound impact on the drug product. The industry now recognizes the importance of focussing on primary packaging in the drug development process. For biologics, new drug products are often launched in vials or syringes, observes Professor Volker Rupertus, senior principal expert for Schott. “Given the complex and sensitive nature of these molecules, the compatibility of the packaging material with the drug product is an important aspect. But it’s also equally important to ensure that the packaging meets machine fill/finish requirements as well as patient requirements, such as the need for self-administration,” he says. “It is unlikely that we will have one packaging solution that covers all drugs,” Rupertus points out. “Therefore, collaboration between the pharmaceutical company and its packaging suppliers (including the elastomer component suppliers), machine vendors, and fill/finish contractors is needed. In fact, it is important to develop the drug product and its appropriate packaging at the same time,” he says.

VanTrieste believes that the earlier all parties are brought to one table (at the latest, prior to clinical studies), the better. He adds that a close collaboration involving all parties will support pre-qualification of packaging combinations and platforms. “Such collaboration will also support the final packaging evaluation for a specific drug market launch,” he says. “Moreover, the close collaboration can pre-define packaging iterations during the lifecycle of a certain drug.”

Packaging suppliers are constantly working on new packaging solutions to meet the needs of more complex and sensitive drug product, notes Hörsch. “During the development process, the packaging suppliers will reach out to the machine vendors to get feedback about the processability of the new packaging on the existing lines,” he explains.

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**In-line force analysis during vial filling**

Smart Skin Technologies has developed a drone-based online pressure monitoring system to measure forces influencing container integrity during the filling process. Online measurements help identify weak points in the filling line. The information can then be used to optimize the process.

The motivation for in-line force analysis was mainly driven by the need to reduce losses in parenteral production. Pharmaceutical manufacturers want to avoid glass defects and interruptions of filling lines but realized that there was insufficient understanding of the problem affecting the production process.

“In-line analysis is all about understanding where on the manufacturing line forces occur that create damage to the product,” says Joe Norris, head of New Product Development at Smart Skin Technologies. “With the help of data, critical areas and opportunities for optimization can be identified. Following the analysis, lines can be modified to reduce the force applied to the vials, syringes, or cartridges to reduce the damage events. Often times, small adjustments such as lowering the edge of a wedge or optimizing the synchronization between moving parts of the line can significantly reduce breakage.”

Smart Skin’s drone system is a vial clone with sensitive surface materials. “Up to 192 force sensors in the surface of the vial-like drone measure force, and other electronics measure how it spins and tilts as it moves through the production line, and where it is subjected to shock,” explains Norris. “The data are transferred to a Microsoft Surface tablet by Bluetooth and with our Quantifeel software, which prepares easily understandable reports. With help of the data, the software can also calculate where scuffing occurs.”

“One drone moves though a certain section of the line at a time,” he says. “After six to 10 rounds, the customers can already identify certain patterns. These patterns can be displayed in heat maps, and additional video material can be used to identify sections where action is needed. Later on, the drones can help to validate whether the corrective measure brought about the desired effect.”

Norris highlights that the system works with vials, syringes, and cartridges. “Each customer receives a customized set of drones from us, depending on the type and size of the packaging that is filled or produced on the respective line. The customer also receives the software along with training, and we help them interpret the data in the beginning. After that, they use the system independently—for example, for quality assurance, after maintenance shut-downs (to ensure a correct restart of the line), for breakage investigations, or line commissioning audits,” he says.

According to Norris, the roots of Smart Skin Technologies lie in the food and beverage industry. The impetus to apply the technology also in the pharmaceutical industry came from Roche in Switzerland in 2015. “The challenge was to ‘shrink’ the drone, which originally had the size of a drinking bottle, to the size of a pharmaceutical vial. This is exactly the reason why this technology, which easily helps to reduce breakage and increase cosmetic quality, is still new for the pharmaceutical industry,” explains Norris.

“During the project, a drone system for parenteral vial filling, inspection, and packaging lines was developed. The system helped Roche to define relevant limits for glass damage,” says Norris. “Roche can really be seen as a pioneer in this field, and other leading pharma companies have followed.”

— Adeline Siew, PhD
Glass or plastic—A question of use

Packaging plays an important role in preserving the stability and quality of pharmaceutical products so that they are safe and effective when patients use them. Selecting the right type of packaging material to use is, therefore, crucial, especially if it is in direct contact with the product. The packaging must not have an adverse effect on the product, but it is also equally important to ensure that the product does not change the properties of the packaging and affect its protective function. Glass and plastic are well-established primary packaging materials for the pharmaceutical industry but they both have their advantages and disadvantages.

Many medicines do well when packaged in both glass and plastic, observes Jens Heymann, senior vice-president, Europe & Asia Tubular Glass, Gerresheimer. “How well glass or plastic tolerates an active ingredient depends on its composition. Drugs must be carefully examined at an early stage, ideally when clinical tests with the primary packaging begin. The pharmacist must ensure that all possible interactions between the contents and the packaging are recorded and assessed for risk,” he explains.

“Depending on the field of application, the pharmaceutical company may decide to use type I, type II, or type III glass, based on the hydrolytic resistance required,” says Heymann, highlighting that Gerresheimer’s range extends from cough syrup bottles made from amber glass to sterile ready-to-fill (RTF) vials made from tubular glass designed for special injectables. “We constantly adapt our production processes to meet increasingly stringent market requirements,” he adds. Gerresheimer’s Gx Elite Vials, for example, are produced using a conversion process that has been optimized to design out the risk of flaws during production (1). Heymann explains that all glass-to-glass or glass-to-metal contact is removed, beginning from tubular glass right through to the final packaging. The Gx Elite Vials have better quality as a result. The highly shatter-resistant vials are durable and free of cosmetic defects. They have a robust structure and their resistance to delamination protects the drug inside (1).

Gerresheimer also has expertise in making glass syringes. In January 2017, Gerresheimer announced the introduction of a new metal-free technology for residue-free cone shaping (2). “The technology allows the syringe’s cone hole to be shaped using ceramic materials instead of metal or a tungsten pin, which leaves behind traces of tungsten that can lead to unwanted reactions with the active ingredient, particularly for biologics,” Heymann says.

In contrast to glass, plastic is shatterproof and lightweight and can be made flexible, soft, or hard depending on the requirements—a versatility that glass cannot offer, notes Jens Friis, vice-president, Europe & Latin America Plastic Packaging, Gerresheimer. “When choosing the appropriate plastic container, it is important to consider whether the drug is solid or liquid and how it is dispensed, taken, or administered,” he says. “Our Duma tablet container, for example, is for solid active ingredients taken orally. This container has already been around for 50 years in a broad and varied range, featuring tamper- and child-proof closures, integrated desiccant, and much more.”

Friis highlights that Gerresheimer recently introduced alternative packaging solutions made from highly transparent cyclo-olefin-polymer (COP) plastic for new alkaline parenteral formulations and toxic drugs. “COP combines many of the properties of glass with the shatter-resistance of plastic,” he points out. “The COP contact surface also improves the stability of highly sensitive medicines, such as the new generation of biopharmaceutical active ingredients, and minimizes the interaction between the drug and the packaging.”

“For specific requirements, Gerresheimer has developed the multi-layer Gx MultiShell Vial made from COP and a polyamide barrier layer,” says Friis. “This combination makes it possible to enhance the vial’s oxygen-resistant properties many times over that of traditional COP monolayer vials.” According to him, Gerresheimer produces plastic syringes in Germany for the Clearject brand, which also uses COP. “Prefillable plastic syringes do not contain any tungsten left over from the production process and are made without any needle adhesive. They are also shatter-proof and customizable,” he explains. “They are similar to glass syringes in terms of their functional properties such as break loose and gliding forces. The highly transparent material makes ideal primary packaging for sensitive medicines for use in oncology, ophthalmology, or other fields of application.”

Heymann points out that for most, deciding between glass and plastic depends on the following questions: How and where will the medicine be used? How will it be dispensed? Who is it for and how will it be administered or taken? “And then, there is still the question of how the medicine is to be bottled,” he adds. “For example, we have agreed with our competitor Nuova Ompi that we will use the same secondary packaging in the form of nests, trays, and tubs to package our Gx RTF vials—which is the well-known Ompi EZ-Fill packaging format. This way the customer can receive identically packaged sterile injection vials from two different manufacturers, which enables them to start filling the vials straight away without the need for any intermediate process steps.”

Glass and plastic complement each other with their specific properties and benefits, notes Friis. “Although the active ingredient is the top priority, many other factors influence the choice of primary packaging,” he says. “One of our key objectives is to increase the efficiency of drugs by ensuring that they are delivered in the most targeted and complete way possible. User-friendliness and safety in application play an important role in everyday use.”

References

—Adeline Siew, PhD
tight geometric tolerances to enable stable and highly efficient processing. The same applies for ready-to-use configurations, with regards to the outer packaging, tubs, and nests.”

**No one-size-fits-all solution**

“As the requirements for drugs are getting more and more diverse with the advent of new therapies, trying to establish one best solution that is applicable to all drug products is not helpful for an industry that wants to reach a cost/benefit optimum,” says Rupertus. “To give you an analogy, this would be like developing a car that has a tremendous acceleration and at the same time, can transport 30 tons of load.” He explains that the challenge is rather to find the best possible solutions for a specific application, and ideally bundle existing technologies into platforms.

“The really interesting packaging solutions today are not about building new technologies, but rather combining technologies,” observes VanFrieste. “Examples are applying existing standards of syringe filling to nest-and-tub configurations for vials and cartridges, or applying proven toughening procedures to tried-and-true borosilicate glass instead of pushing for change in the glass type.” He adds that changing the glass type would come with high testing work for a holistic risk assessment as well as regulatory effort for re-registration.

**Customer requirements**

Despite interest in other novel materials, borosilicate glass is still regarded as the preferred primary packaging material for parenteral drugs due to its long track record and the large amount of available data. Schott asked customers what they consider as the most important aspects with regards to the packaging container of their drug products. “The vast majority underlined that they want to base any packaging decision on long-term scientific data to minimize any safety risk for the patient and that they want to keep regulatory efforts to the minimum,” says Rupertus.

“An important aspect is the high quality of the glass surface to prevent damage and breakage,” Hörsch highlights. “During the whole process, various forces, such as heat and pressure impacts, can influence the stability of the glass object. Microcracks or scratches, which are already in the glass, can then result in potential breakage of the glass and compromised efficiencies of the processing equipment.”

“The most important requirements I see for glass containers are glass strength, low particle counts, critical dimensions, and cosmetic appearance,” says VanFrieste.

**Cosmetic quality**

According to Rupertus, cosmetic quality (i.e., accurate dimensions and flawless surfaces) is the most prevalent demand among its customers. The dimensions are important for several reasons. “First, the more accurate the vial, syringe, or cartridge, the more smoothly it will run on the production line,” he explains. “Second, tight tolerances, for example, in inner diameters, lead to improved container closure integrity and gliding force in the case of syringes, as the fit between the elastomer components (e.g., stopper) and the container is much better:”

“A flawless outer surface has, in fact, a huge impact on the reduction of breakage,” says Rupertus, who has undertaken extensive studies on glass surface characteristics. “Glass has a remarkably high internal strength. Its weak points are small cracks on the surface or edges. These micro-defects can spread inward as mechanical stress increases, leading to sudden fractures. Looking at it the other way around, vials of high cosmetic quality with an intact surface are already at least twice as resistant to breakage.”

Rupertus points out that breakage is mainly a problem with old filling lines, considering that surface defects are mostly caused by production or handling. “Newer lines come with improved handling technologies, and with the switch to ready-to-use filling lines, where the packaging is safely fixed in a nest, we no longer have this problem,” he says. “A variety of technologies are available to improve existing lines [see Sidebar about sensor technologies from Smart Skin]. We know of a variety of cases where minor adjustments have already made a huge difference.”

Rupertus highlights that for the vast majority of applications, improved cosmetic quality (and thus reduced breakage risk) plus line optimization are an adequate solution. “In cases that require stronger break resistance (e.g., toxic drugs), proven chemical toughening procedures can achieve compressive stress in the glass surface, hence, preventing cracks from propagating and making the respective glasses more break-resistant. This method is an industry standard. Schott and others, for example, have been offering chemically toughened borosilicate glass cartridges for some time. This procedure can also be applied to produce vials with higher break resistance,” he says.

Rupertus explains that further improvements related to particles and/or pre-damages, such as scratches or chips, can be achieved with better forming technologies combined with automated camera systems/inspection technology. “Such technologies also help to avoid scratches and reduce particle load significantly,” he notes.

“To further evolve this, packaging suppliers and machine manufactures can form close ties and work on improved glass handling, advanced transport and logistic concepts, standardized interfacing, and Big Data approaches to name a few.”

**Conclusion**

“With more patients around the world gaining access to healthcare, supply chains are becoming more complex,” says Rupertus. “For suppliers, concentrating on their own processes no longer suffices. While this complexity certainly poses many challenges and calls for new ways of collaboration, there is also a positive side to it—working closely can indeed fuel supplier-enabled innovation. Packaging serves as the interface to the patient and is the key to achieving dosage accuracy and enabling self-administration. Therefore, working closely with packaging, filling line, and elastomer partners can help pharma companies to market drugs in a faster and safer way.”

**Reference**

1. EvaluatePharma, “World Preview 2017, Outlook to 2022,” June 2017. PTE
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For solid-dosage forms, capping is a primary operation on the packaging line. Cappers and related equipment integrate seamlessly with up- and downstream systems, ensure proper application and removal torque, maximize overall equipment effectiveness (OEE), and offer quick changeover across a range of cap sizes and styles.

Caps, or closures, not only close the container and protect the product, but often offer additional functionality such as easy dispensing, child resistance, tamper evidence, and shelf-life protection. Demand for additional functionality, particularly child-resistant (CR) and tamper-evident designs, is helping spur a 5% compound annual growth rate through 2020 for pharmaceutical caps and closures, according to a market study from Technavio (1).

Increasing shelf-life
To address stricter requirements related to drug stability, there’s considerable action in closures with enhanced shelf-life protection capabilities. Activ-Seal scavenging closures from CSP Technologies streamline the packaging process for products needing added protection from relative humidity (RH), oxygen, or other gases by building the scavenger into the closure, thereby eliminating the need to purchase and insert a scavenging canister or sachet into each bottle, which also avoids the risk of accidental ingestion. “Depending on the customer’s need, we can maintain target RH that is between a designated set of ranges or draw down close to zero,” says James McGetrick, associate director of Business Development for CSP Technologies. Launched in 2016 and designed to work with existing caps, containers, and packaging equipment, several pharmaceutical manufacturers are completing testing of Activ-Seal closures. “We expect a commercially approved product to enter the market soon,” he adds.

Another built-in scavenger, the Silica Gel Capsule from Italy’s Bormioli Rocco, integrates scavenger and closure. “This solution allows for improvements both in terms of machinability and patient safety,” explains Anna Malori, a member of the business development staff at Bormioli Rocco. “Because the cap contains the desiccant, no additional filling processes are required, and filling times are greatly reduced. Furthermore, this solution avoids the risk of accidental ingestion that can occur with silica gel packets.”

Senior-friendly CR closures
Greater efficiency and sustainability benefits prompted the development of a one-piece, thread-free polypropylene closure by Comar. Designed to replace traditional two-piece push-and-turn CR closures, the senior-friendly SecureCap QuarterLoc closure reduces part weight and manufacturing complexity and offers a potential cost savings up to 25%. The bayonet-style neck finish enables application and removal of the closure in a quarter turn and eliminates concerns about application torque, cross-threading, and cocked closures. Compatible with CR and non-CR containers, the closure can be manufactured in standard sizes. It does not require a liner but can accommodate a pulp-backed, glued-in foil induction liner and is compatible with conduction liners, which are heat-sealed in place before the cap is applied. The closure can be applied on standard capping equipment and will not back off after application (2). Although there are no commercial users yet, Sue Benigni, business segment director at Comar notes, “the closure mold is under construction. We have been doing customer trials for gummy vitamin products with several of the major manufacturers.”

Applying consistent torque
Although torque measurement is not a factor when applying the QuarterLoc closure, it’s a critical parameter for many other closure styles. “Manufacturers are moving toward a zero-defect philosophy where applying caps produces reject rates less than 0.5%, and every cap torque application is measured with torque profile monitored for consistency, standard deviation, and conformity,” notes Alan Shuhaibar, president of BellatRx.

Monitoring is particularly important on lines with induction sealing. “To achieve a proper seal, you have to have the proper applied torque,” explains Omar Azam, inside sales manager at NJM Packaging, a ProMach Product Brand.
also maximizes product quality by more consistent torque values. It even when the cap stops turning. This with the rotating speed of the closure, one drive synchronizes the linear pairs of belts gently rotate and tighten of each induction seal.

Technologies, can verify the integrity using infrared technology from DIR seals. Another inspection option, skewed caps and missing induction identify containers with missing or protecting quality, the beltorque capper specification,” says Azam. To further so we can make sure each one is in every container as the cap is applied “We can measure applied torque on under or over pre-set thresholds. to remove capped bottles that are removed the cap for the first time, the seal can be hard to remove. A pull tab on the Easy Peel induction liner from Bormioli Rocco solves that problem. Compatible with all of the company’s closures and bottles for solid doses, the tabbed design eliminates the need to use potentially dangerous tools to remove the liner without changing its ability to protect tablets or capsules from humidity, oxygen, and other environmental factors. Induction liners are fused on bottle orifices by induction sealers. Like many packaging machines, today’s induction sealers use energy more efficiently and require less power than their predecessors. Other features include touch-screen control and integrated cap inspection. “The reason cap inspection is so integral to the success of induction sealing is two-fold,” explains Mark Plantier, vice-president of Marketing at Enercon Industries. “A liner must be present in each cap, and the cap cannot be misapplied in a cocked fashion. Cap inspection is able to detect these variations. Prior to this innovation, cap inspection was controlled by an independent control system. By integrating it both mechanically and electrically into the induction sealer, packagers are able to quickly set up their systems and rely on a single control and diagnostics for both cap inspection and sealing.” Changeover is simpler too. For example, an all-in-one sealing head, designed by Enercon for contract packagers, provides operators with indicators and positive locking mechanisms for properly positioning the head for each application.

Enercon’s Deluxe Cap Inspection package provides even more control. An advanced laser-light curtain for cocked cap detection allows users to set specific tolerances for detecting out-of-spec cap application. The system also offers remote control and monitoring of all data collected by the induction sealer.

To ensure induction sealing performs at the highest OEE possible, Plantier advises looking at the process holistically. Equipment should be designed for the specific sealing application, and induction sealing experts should be involved early in the design process for the cap and bottle. “The type and range of caps, bottles, liners, and line speeds will help the induction sealer manufacturer recommend the best sealer and sealing head for the application,” says Plantier. With equipment properly specified, the original equipment manufacturer should provide detailed setup instructions including alignment, air gap, line speed, and sealing power. Induction sealing success, however, is dependent on external variables, including the quality of the cap, liner, and container materials, as well as the capping process itself. “Properly torqued caps are required for induction sealing, and in fact, improperly torqued caps are the most frequent cause of partial or failed seals,” concludes Plantier.

Improving induction seals
Beneath the flip-top cap, an induction seal often provides tamper evidence and protects product quality. Unfortunately, when a consumer removes the cap for the first time, the seal may be hard to remove. A pull tab on the Easy Peel induction liner from Bormioli Rocco solves that problem. Compatible with all of the company’s closures and bottles for solid doses, the tabbed design eliminates the need to use potentially dangerous tools to remove the liner without changing its ability to protect tablets or capsules from humidity, oxygen, and other environmental factors.

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References
Implications of the United Kingdom’s exit from the European Union (EU) cast a shadow over Europe’s bio/pharmaceutical market in 2017, as well as its prospects for 2018. While one major question—the relocation of the European Medicines Agency—was answered in late 2017 with the announced move to Amsterdam, many unresolved issues, including regulatory approvals and supply chain monitoring, remained (1).

In 2017, the European Medicines Agency’s (EMA’s) Committee for Medicinal Products for Human Use recommended marketing authorizations for 92 innovator and generic drugs, an increase from 81 authorizations in 2016 (2–3). US drug approvals hit record levels; 46 new molecular entities were approved in 2017 compared with 22 in 2016 (4). This big rebound, plus the approval of the first gene therapies, created a more positive outlook in the United States.

Regulatory changes pending
As Brexit negotiations defining the terms of the UK’s departure progressed, an agreement for cooperation between regulatory authorities that could reduce inspection bottlenecks was launched. A mutual recognition agreement, effective 1 Nov. 2017, enables drug regulatory authorities of Austria, Croatia, France, Italy, Malta, Spain, Sweden, the UK, and the US to use each other’s good manufacturing practice (GMP) inspections of pharmaceutical facilities (5).

Sterile drug manufacturers faced major changes in operating procedures; Annex 1, Manufacture of Sterile Medicinal Products of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) and EU GMP guide is under revision (6). Annex 1 has been updated since it was first published in 1971 but has not had a full review. The purpose of the revision, according to an European Commission announcement, is to add clarity, introduce the principles of quality risk management, include new technologies and processes, and change the document structure to a more logical flow. Proposed changes include the introduction of sections on utilities, environmental and process monitoring, and a glossary.

The proposed revised version was prepared in cooperation with, and is subject to, parallel public consultation with the World Health Organization and PIC/S. The consultation document was issued on 20 Dec. 2017; the European Commission is collecting comments until 20 March 2018.

Great expectations
Analysts at Evaluate Pharma (7) note that scientific breakthroughs improve the lives of patients and can richly reward the drug’s creators. The successes need to continue, however, to keep investors interested in the market. The bar for success is set high with rapid progress during the past few years, Evaluate Pharma reports, and disappointments would remind investors that in biopharma, “failure is a fact of life.”

Through the third quarter of 2017, pharma and biotech transactions declined for a second year compared with the active markets of 2014 and 2015, according Evaluate Pharma (7). In the US, the decline was attributed to uncertainty over tax law changes.

In 2018, companies with legacy drug products in large therapy areas may seek mergers and acquisitions to refill depleted pipelines. In the Evaluate Pharma report, experts noted that early-stage companies developing immune-oncology drugs were overvalued, creating a “seller’s market.” The valuations of large-cap biotech companies were depressed, the report argued, creating opportunity for cash-rich pharma companies to make large acquisitions.

Strong financial markets also could spur more initial public offerings and small biotechs may also look to independently fund later-stage development, the report authors note. Venture funding, which slowed in 2017, but could pick up again, the report suggests, benefiting start-up companies in Europe. A competitive market in the US has pushed up prices for acquisitions; investors are looking to Europe for alternative opportunities (7).

Cost of innovation
Although promising platforms such as gene therapies are emerging, the challenge for bio/pharma is to develop these platforms in an efficient way to create “near-term value for all stakeholders,”
according to the authors of Deloitte’s annual study on industry return on investment (8). The report—based on analysis of estimated return on investment from late-stage pipelines of 12 large-cap biopharma companies—noted that projected R&D returns continued to decline from 10.1% in 2010 to 3.7% in 2016 and 3.2% in 2017.

Perspectives from bio/pharma personnel
Pharmaceutical development and manufacturing experts shared their opinions about the state of the industry and prospects for 2018 in the 2017 Pharmaceutical Technology/Pharmaceutical Technology Europe annual employment survey (9). Respondents from around the globe shared similar perspectives about employment-related prospects, but also expressed varying opinions about business prospects for bio/pharma.

Bio/pharma business activity in Europe was up in 2017, the survey respondents reported. One-half of the EU-based respondents reported an increase in business at their company over the previous year, a significant jump from 42.3% in 2016 (10) and 40% in 2015; only 10.9% reported a decrease. In comparison, only 35.6% of the global audience of respondents reported an increase in business in 2017; 16% reported a decrease.

The positive trends in Europe continued in other business areas at bio/pharma companies, as compared with observations from the global audience. Companies hired additional employees (37.5% EU vs 22.67 global), expanded business operations (18.8% EU vs. 11.1% global), and experienced less downsizing (12.5% EU vs 18.2% global). In line with the reports of increased business, the EU-based respondents also noted that more tasks previously done in-house were outsourced to contract service providers (17.2% EU vs 11.1% global).

Mixed outlook
The positive feelings from 2017 fueled an optimistic outlook from EU-based bio/pharma employees for 2018; 62.5% of the respondents predicted that their company’s business would improve in 2018, up from 50.4% for 2016. Less than 10% said business would decline. In contrast, only 52.9% of the respondents from the global audience said business at their companies would improve and 14.7% predicted business would decline.

The EU-based audience, however, was less positive in their outlook for the bio/pharma industry in general for 2018: 37.5% said business would improve in 2018, down from a prediction of 46.4% for 2017. Almost half of the global audience surveyed expected business to increase.

Predictions for business growth in the bio/pharma industry as a whole over the next five years were more optimistic and similar to responses in 2016. Nearly two-thirds (64.1%) of the EU-based respondents predicted that business will improve; however, 12.5% expect business to improve overseas, but not domestically.

US taxing decisions: R&D, M&A, or investor windfall?

In the United States in 2017, the bio/pharma industry witnessed a record number of drug approvals including the first gene therapies and a digital pill, a new commissioner at the US Food and Drug Administration, and a major overhaul to the US corporate tax structure. Unfinished business—open questions about the fate of the US healthcare system, an unresolved federal budget, and ongoing debate over drug pricing—have extended the air of unpredictability into 2018 for bio/pharma companies in the US and around the world.

Thanks to the overhaul of the tax system enacted in late December 2017, US-based bio/pharma companies started 2018 with a lower corporate tax rate, lower taxes on income earned abroad, and simplified rules for expensing new investment purchases.

The tax law overhaul had one negative: the orphan drug tax credit was reduced from 50% to 25% of qualified research and clinical testing activities. What biopharma companies will do with the tax savings or repatriated funds—invest in R&D, return it to stockholders, or shop for acquisitions—was not clear as 2018 began. While the intent of tax law changes is to expand investment and create more jobs in the US, companies may continue to invest overseas. A previous “tax holiday” for repatriated funds in 2004 resulted in minimal job creation; analysts and critics of the tax cuts expect a similar result with this round of cuts (1).

References
The United States is facing an opioid crisis. The US Food and Drug Administration has expressed concern about the growing epidemic of opioid abuse, dependence, and overdose, and part of its action plan includes a call to pharmaceutical manufacturers to develop opioid formulations with abuse-deterrent properties (1). As a result, there is increasing interest in the development of abuse-deterrent formulations as the technologies to prevent abuse among patients and recreational abusers continue to advance rapidly.

"Generally speaking, abuse-deterrent formulations should prevent drug abuse, but maintain clinical benefit and patient compliance," says Michael DeHart, associate director, Pharmaceutical Development, Metrics Contract Services. "In other words, incorporating excipients to prevent drug abuse should not alter the bioavailability of the API or increase the tablet/capsule size dramatically."

According to DeHart, one of the biggest challenges in developing an abuse-deterrent opioid formulation is that formulators are sometimes formulating from a reactive perspective. "A similar comparison can be made to how antivirus software developers must sometimes react to, or address, hackers who have already released a virus," he says. "Drug abusers are highly resourceful and can generally 'hack' a formulation to get what they want."

Abuse-deterrent approaches
Current products on the market that contain abuse-deterrent labelling approved by FDA fall into two categories, highlights Angela Moore, scientist, Analytical Development, Alcami. One is based on a physiochemical abuse-deterrent approach and the other combines the opioid with an antagonist. "Physiochemical abuse-deterrent properties include products that are formulated to resist crushing, chewing, and physical manipulation. They contain excipients that will gel upon contact with solvents to make them difficult to inject intravenously," she explains.

One of the more common excipients used to impart abuse-deterrent properties is polyethylene oxide (PEO), observes DeHart. "PEO can be cured or processed through hot-melt extrusion so that it cannot be crushed," he says. "Grunenthal’s abuse-deterrent Intac Technology is based on this approach." Tablets produced using Intac Technology have higher mechanical strength and are, therefore, resistant to crushing (2). An additional advantage is the low extractability of the active drug from the tablet in a wide range of solvents (2). "This low extractability is because PEO swells when exposed to various solvents," DeHart says. The gelling of the polymer creates a viscous mass that is difficult to draw into a syringe, hence, raising the hurdles to drug abuse. DeHart notes that Purdue Pharma uses PEO in their reformulated OxyContin tablets.

"Opioid/antagonist products, on the other hand, contain the active opioid intended for therapeutic use as well as a sequestered antagonist, so that if the product is manipulated intentionally, it will release a chemical that will prevent the user from feeling the euphoric effects of the opioid," Moore points out.

DeHart cites Pfizer’s Embeda as an example of an opioid formulation containing an antagonist. "In the case of Embeda, inactive naltrexone (i.e., the antagonist) is formulated with morphine sulfate in the capsules. If the capsules have been adulterated for potential abuse, the antagonist would become bioavailable and prevent any kind of abuse," he says. "Opioid formulations may also include excipients such as sodium lauryl sulfate that can cause irritation when crushed and snorted."

According to Moore, there are many considerations for manufacturers developing abuse-deterrent opioid formulations. "Most importantly, the product must be considered safe and effective, and it must adhere to all FDA manufacturing and testing guidelines," she stresses. "From a chemistry and biologic perspective, the product must resist dose dumping and abuse, but still release the active ingredient when ingested as intended. From a commercial viewpoint, one of the key considerations is to develop a product that has a competitive advantage over those already on the market."

She explains that a company must differentiate its product in such a way that doctors will want to prescribe the new product over other available...
alternatives. She adds that insurance companies must also be convinced that the new product is worth paying more money for compared to cheaper products that do not contain abuse-deterrent formulation properties.

Evaluating abuse-deterrent formulations

The current FDA guidelines (3) for determining the effectiveness of abuse-deterrence of a drug product involve four main studies, termed Category 1, 2, 3, and 4. “Category 1 testing involves laboratory manipulation and extraction studies,” says Moore. “In these studies, the product is evaluated and compared to currently marketed formulation(s) for the ability to defeat or compromise the abuse-deterrent properties. This testing is done in vitro and provides the physical characteristics of the product and its ability to resist crushing, grinding, melting, and to resist nasal abuse. Extraction studies provide information on the product’s ability to isolate the antagonist, or resist abuse by injection, or, in larger volumes, resist abuse by ingestion,” she explains.

“Category 2 testing involves pharmacokinetic studies in healthy humans. The product’s in-vivo properties are evaluated by comparing an intact formulation against the manipulated formulation through one or more routes of administration. Comparator products are also evaluated for comparison,” says Moore. She adds that Category 3 testing evaluates the clinical abuse potential of the product. “These are large, complicated in-vivo studies that are generally conducted with recreational drug users as test subjects. These test subjects are screened prior to the study to ensure that they are able to distinguish between the active drug and a placebo in a drug abuse setting. In these studies, the test subjects are provided the drug product being developed and suitable comparators. The drugs are administered through the route of abuse that is being studied (i.e., oral or intranasal) and the patients provide not only pharmacokinetic data, but also subjective data on the drug liking (how high they are) and if they would take the drug again,” she explains.

Moore highlights that Category 4 assessment is a post-approval study that determines if the product has resulted in meaningful reductions in abuse, misuse, or adverse clinical outcomes (addiction, overdose, and death). “These evaluations are conducted by the product manufacturer,” she says, pointing out that currently, there are no products on the market that qualify for the Category 4 label for abuse-deterrence.

“Recently, one of the more common tests that we have seen being used to evaluate the effectiveness of abuse-deterrent formulations is its syringeability,” DeHart notes. “Syringeability looks at how much opioid can be extracted from a tablet using heat, agitation, and in small volumes of water to see if it can be pulled through a syringe.”

According to DeHart, drug products that are susceptible to snorting should be evaluated for crushability and particle size distribution. He adds that tablets should also be evaluated to determine if dose dumping can be prevented. “Dose dumping typically occurs when painkillers are consumed with alcohol,” he explains. “It is, therefore, important to evaluate opioid release from drug products in dissolution media with various concentration of ethanol.”

While the pharmaceutical industry has a crucial role to play in developing opioid formulations that are more resistant to abuse and manipulation, the opioid crisis can only be tackled effectively if FDA, governments, policymakers, healthcare providers, patients, and their families to work together, as pointed out by FDA Commissioner, Scott Gottlieb (4).

References
4. FDA, “Statement from FDA commissioner Scott Gottlieb, MD, on the Trump Administration’s Important Efforts to Address the Opioid Crisis,” 26 Oct. 2017. PTE

FDA Commissioner says packaging innovations can help address opioid crisis

The United States Food and Drug Administration Commissioner Scott Gottlieb, MD, said that reducing the overall exposure to opioid drugs is a crucial part of preventing addiction, and that FDA is exploring further how opioid drug products are packaged, stored, and disposed of. In a 30 Oct. 2017 statement (1), he noted that FDA is considering a number of packaging solutions: “For example, it’s possible that a defined, short-term supply of medication could be packaged in a manner that limits the number of pills dispersed. This might be achieved, for example, through a blister pack that has a defined duration of use that might be for only a limited number of doses. Other packaging innovations could make it easier to track the number of doses that have been taken. Still other options could work to improve storage and encourage prompt disposal to reduce the available supply and reduce the risk for third-party access, such as a child accidentally ingesting pills found in a medicine cabinet. There are also technologies that could allow healthcare providers, pharmacists, or family members to monitor patient use of prescription opioids.”

FDA held a public workshop, “Packaging, Storage, and Disposal Options To Enhance Opioid Safety—Exploring the Path Forward,” on 11–12 Dec. 2017 in Silver Spring, MD. The goals of the workshop, according to Gottlieb, encompass three key areas: “First, we need to define the specific problems that these types of packaging and disposal solutions can help address. Second, we want to more clearly define the guiding principles that the scientific community should consider in designing product features that achieve these possible solutions. Finally, we’ll better define the types of data needed in order to evaluate how these solutions are working.”

Reference

Pharmaceutical Technology Europe JANUARY 2018 25
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A new algorithm uses a statistical approach to critical process parameter assessment, allowing for faster, more consistent, and less subjective critical process parameter quantification, visualization, and documentation.

Removing Subjectivity from the Assessment of Critical Process Parameters and Their Impact

Fasheng Li, Brad Evans, Fangfang Liu, Jingnan Zhang, Ke Wang, and Aili Cheng

Determining critical process parameters (CPPs) is vital to defining the control strategy for drug substance and drug product manufacturing processes (1). Deciding the criticality of a process parameter, however, can often become a subjective exercise, resulting in long discussions within product development teams as well as back-and-forth communication with government regulators during new drug application review.

A data-driven statistical approach was developed (2) to help reduce subjectivity and debate in determining the criticality of process parameters in the manufacturing of drug substance and drug product. The approach uses the distance of a critical quality attribute (CQA) from its quality limit, together with the estimated parameter effect size, to designate the criticality of a process parameter.

The method relies on straightforward calculations. However, performing these calculations manually can be time-consuming and error-prone when the statistical model involves multi-factor interactions and higher order parameter effects. To incorporate this systematic approach into daily practice, statisticians have developed a web-based computational tool that uses this method.

This article examines how the algorithm was developed, focusing on the calculation of process parameter effect size on a CQA. It also discusses how analytical and numerical solutions of parameter effect size resulted from conventional linear models.

Using grid search to develop a numerical approach makes the algorithm flexible and simple enough to cope with all types of linear models that could have main effects, as well as higher order interaction and parameter effects. In addition, the resulting tool supports the linear model with transformation and provides a bias correction for modeling responses in the transformed scale.

A statistical approach to identifying CPPs

The assessment of CQAs and the control of the CPPs that impact these attributes are crucial to the overall control strategy for biopharmaceutical product manufacturing (2).
The International Council for Harmonization (ICH) Q8(R2) (3) describes a CPP as “a process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure that the process produces the desired [level of] quality.”

There are many different approaches for assessing process parameter criticality. Statistics, typically using data from a designed experiment, plays an important role in these evaluations. However, assessing the impact based solely on statistical significance (e.g., \( p \)-value) is inadequate, because it does not take into account the strength of the relationship between variables and the process risk.

The new statistical approach (1) helps determine when a statistically significant relationship between a process parameter and a critical quality attribute imposes a practical concern, based on how close the data are to the target limit. Figure 1 illustrates the approach, highlighting its three main components: a statistically significant relationship, a Z score, and use of the 20% rule. The Z score for a CQA \( y \) with a one-sided quality target limit \( L \), is calculated as shown in Equation 1.

\[
Z = \frac{|\text{mean}(y) - L|}{s},
\]

[Eq. 1]

where \( s \) is the estimated standard deviation of \( y \).

The Z Scores can be applied to any CQA with either a one-sided or a two-sided target limit. For a two-sided limit, the Z score is determined by the limit closest to the mean.

The value of \( Z \) indicates how far, in standard deviation units, the data are from the quality limits. A large \( Z \) score is shown in the middle plot in Figure 1. Because the whole set of collected data is far from the lower quality target limit, the process is at low risk of producing out-of-limit (OOL) results.

The right-hand plot in Figure 1, however, shows data with a low Z score. This shows that this set of data is close to the targeted limit, and, thus, that the process is at higher risk of producing OOL results.

In established practice, Z scores of two and six are used as cutoff values in determining the criticality of process parameters. For example, if the data have a Z score greater than six, no CPP will be assigned to the CQA because the process is at low risk. Moving any parameter over its proven acceptable range will not compromise product quality.

If the data of a CQA are close to its target limit, however, and their Z score is less than two, it is generally appropriate to assume that all statistically significant parameters are CPPs. If the data of a CQA have a Z score between two and six, all statistically significant effects are potential CPPs and the data will be subject to the 20% rule (i.e., if the parameter’s impact is greater than 20% of the quality target range [QTR], that process parameter will be considered a CPP). The QTR is the window where we expect or need the quality attribute to land at that step in the process. The CTR can be defined as \([\text{upper limit} - \text{min}(y)]\) or \([\text{max}(y) - \text{lower limit}]\) for one-sided target limit, and \([\text{upper limit} - \text{lower limit}]\) for two-sided target limits.

If the parameter is determined not to have a statistically significant relationship to a CQA, or its effect size is less than 20% of QTR, subject matter experts should review the established science related to this process parameter in the context of the entire control strategy before designating this parameter as non-critical.
Following a holistic review of control strategy, most parameters that are found to be insignificant will be defined as non-critical process parameters. Exceptions would only be made for parameters where significant scientific evidence suggests that they will have an impact on a CQA and where designating them as critical would improve the overall control strategy. However, such cases would be relatively rare.

Parameter effect size

The effect size of a process parameter provides an estimate of the maximum change in a product quality attribute that is contributed by that process parameter. Parameter effect size calculation is carried out through the established functional relationships between process parameters and quality attributes. This paper focuses on the functional relationship (i.e., the statistical model). A conventional statistical linear model can provide an analytical solution of the parameter effect size. When the model has higher-order terms, however, the analytical solutions are in more complex forms, and a practical computational algorithm would be needed to perform such evaluations routinely.

A second-order linear model is commonly used in statistical design of experiments to reveal the functional relationship between process parameters and a quality attribute. The general form can be expressed as shown in Equation 2:

\[ y = \beta_0 + \sum_{i=1}^{n} \beta_i x_i + \sum_{i=1}^{n} \sum_{j>i}^{n} \beta_{ij} x_i x_j + \epsilon, \]  

[Eq. 2]

where \( x_i (1 \leq i \leq n) \) represents the \( i \)th process parameters on [-1, 1] with center point 0, \( y \) represents the quality attribute, \( \epsilon \) follows from the normal distribution \( N(0,\sigma^2) \), \( \beta_i (1 \leq i \leq n) \) is the regression coefficient corresponding to the first order term \( x_i \), and \( \beta_{ij} (1 \leq i \leq j \leq n) \) is the regression coefficient corresponding to the second order term \( x_i x_j \).

Without loss of generality, let us consider how to estimate the effect sizes of \( x_i \) under four different scenarios. In the first three cases, the effect sizes have explicit analytical solutions, and the corresponding expressions are summarized in Table I. The effect sizes of other process parameters can be estimated similarly.

**Table I: Estimated effect size for parameter \( x_i \) under different scenarios assuming the regression model (1).**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Estimated effect size for parameter ( x_i )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only linear effect but no interaction with other parameters</td>
<td>( 2</td>
</tr>
<tr>
<td>Linear effect and interaction with some parameters</td>
<td>( 2(</td>
</tr>
<tr>
<td>Quadratic effect and no interaction with other parameters</td>
<td>( 2</td>
</tr>
<tr>
<td></td>
<td>( + \max\left(\beta_{ii} + \beta_i^2 \frac{\beta_{ii}^2}{4\beta_{ii}^2}, \beta_{ii} - \beta_i \right) )</td>
</tr>
<tr>
<td></td>
<td>( + \frac{\beta_{ii}^2}{4\beta_{ii}^2} ) \times \left(\frac{\beta_i}{2\beta_{ii}}\right) \leq 1 )</td>
</tr>
<tr>
<td>Quadratic effect and an interaction with other parameters</td>
<td>Same as above but evaluated at all combinations of +/- 1 for all parameters involved in an interaction with ( x_i )</td>
</tr>
</tbody>
</table>

A second-order linear model is commonly used in statistical design of experiments to reveal the functional relationship between process parameters and a quality attribute. The general form can be expressed as in Equation 2:

\[ y = \beta_0 + \sum_{i=1}^{n} \beta_i x_i + \sum_{i=1}^{n} \sum_{j>i=1}^{n} \beta_{ij} x_i x_j + \epsilon, \]

where \( x_i (1 \leq i \leq n) \) represents the \( i \)th process parameters on [-1, 1] with center point 0, \( y \) represents the quality attribute, \( \epsilon \) follows from the normal distribution \( N(0,\sigma^2) \), \( \beta_i (1 \leq i \leq n) \) is the regression coefficient corresponding to the first order term \( x_i \), and \( \beta_{ij} (1 \leq i \leq j \leq n) \) is the regression coefficient corresponding to the second order term \( x_i x_j \).

Without loss of generality, let us consider how to estimate the effect sizes of \( x_i \) under four different scenarios. In the first three cases, the effect sizes have explicit analytical solutions, and the corresponding expressions are summarized in Table I. The effect sizes of other process parameters can be estimated similarly.

**Figure 2(i)** shows a contour plot of predicted values for the fitted model \( \hat{y} = 8 + 5x_1 - 2x_2 \). The maximum change of \( y \) due to \( x_1 \) is 10 (regardless of \( x_2 \)) and the change due to \( x_2 \) is 4 (regardless of \( x_1 \)).

**Figure 2(ii)** shows a contour plot of predicted values for the fitted model \( \hat{y} = 8 + 5x_1 - 2x_2 + 4x_1 x_2 \). The maximum change of \( y \) due to \( x_1 \) is 2 given \( x_2 \) fixed at -1 (bottom edge); whereas the maximum change is 18 when \( x_2 \) is +1. Taking the larger value, the effect size of \( x_1 \) is estimated to be 18. Visually, these are simply the changes along the top and left edges, respectively. For the change due to \( x_2 \), the left edge shows a change of 11 while the right edge shows a change of 4. Therefore, the effect size for \( x_2 \) is 11.

**Figure 2(iii)** shows a contour plot of predicted values for the fitted model \( \hat{y} = 80 - 5x_1 + 4x_2 + 4x_2^2 \). The maximum change of \( y \) along \( x_2 \), given \( x_1 = -1 \), is the difference between the largest predicted value of 93 at \( x_2 = 1 \) and the smallest predicted value of 84 at the inflection point -0.5. The maximum change is 9.

When \( x_1 = 1 \), the corresponding values are 83 and 74, still resulting in a max change of 9. It is necessary to find a single inflection point. Switching to \( x_1 \), the maximum change is 10 (regardless of the value of \( x_2 \)).

**Figure 2(iv)** is similar to **Figure 2(iii)**, but now includes an interaction along with a quadratic effect. This fitted model is \( \hat{y} = 80 - 5x_1 + 3x_2 + 3x_1 x_2 + 4x_2^2 \). Due to the interaction, the inflection points must be found along the both left edge and the right edge.
Along the left edge, the maximum change is 4, with 89 being the prediction at both the lower left and lower right and 85 being the minimum, at the inflection point of 0.5.

Along the right edge, the inflection point occurs at \( x_1 = 0.75 \) and the change of 12.25 occurring along the right edge, based on a minimum of 72.75 at the inflection point and a maximum of 85 when \( x_1 = 1 \).

**Effect size with transformed quality attribute**

Transformation of a quality attribute is often used to improve the model fit or to correct violations of model assumptions. In the transformed scale, the effect size of a process parameter for an attribute can be obtained formally by applying the formulas previously introduced. If the situation calls for examining the change of a quality attribute in its original scale, the effect size must be evaluated on a case-by-case basis, depending on the transformation.

Assume that the model is constructed based on a monotone-transformed response, denoted as \( g(y) \), where \( g(\cdot) \) is the transformation function. The second-order linear model with transformation can be written as shown in the following expression, labeled **Equation 3**.

**Figure 2:** Contour plots of predictions for four examples.

(i) with only linear effects of two parameters on the quality attribute
(ii) with interaction effect of two parameters on the quality attribute
(iii) with quadratic effect of parameter \( x_1 \) on the quality attribute
(iv) quadratic with two factor interaction
(v-vi) For model \( \log_{10}(y) = 2 + 0.5x_1 + x_2 \)
(v) The prediction of \( \log_{10}(y) \) across the design space

![Contour plots of predictions for four examples.](image-url)
where $\varepsilon \sim N(0, \sigma^2)$.

Without loss of generality, consider only the calculation of the $x_1$ effect size. By definition, the effect size of parameter $x_1$ is the maximum change in predicted response due to parameter $x_1$ when the other $(n-1)$ dimensional vector $(x_2, \ldots, x_n)$ is fixed at any point in the parameter space $[-1, 1]^{n-1}$. Thus, the effect size due to parameter $x_1$ may be found by solving the following optimization problem, defined in the following expression (Equation 4):

\[
\text{max}_{-1 \leq x_1, \ldots, x_n \leq 1} \{ \text{max}_{-1 \leq x_1, \ldots, x_n \leq 1} f(x_1, \ldots, x_n) - \text{min}_{-1 \leq x_1, \ldots, x_n \leq 1} f(x_1, \ldots, x_n) \},
\]\n
where $f(x_1, \ldots, x_n)$ denotes the prediction of response at a given design point $(x_1, \ldots, x_n)$. Manually solving this optimization problem is complicated. Due to transformation, the parameters $x_2, \ldots, x_n$ can have an influence on effect size regardless of the model form. To illustrate this point, consider a simple linear model with logarithm transformation of $y$ as expressed in Equation 5.

\[
\log(y) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \varepsilon, \quad \text{[Eq. 5]}
\]

Table II: Estimated mean of response with and without bias correction.

*Note that $\mu$ is the prediction of transformed response $g(y)$, and $\sigma$ is the standard deviation of error. $\varphi(\cdot)$ is the probability density function of the normal distribution with mean $\mu$ and standard deviation $\sigma$.

<table>
<thead>
<tr>
<th>Transformation</th>
<th>Estimated mean $E(Y)$ without bias correction</th>
<th>Estimated mean $E(Y)$ with bias correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>log $(Y)$</td>
<td>exp ( $\mu$ )</td>
<td>$\exp ( \mu + \frac{\sigma^2}{2} )$</td>
</tr>
<tr>
<td>$\sqrt{Y}$</td>
<td>$\mu^2$</td>
<td>$\mu^2 + \frac{\sigma^2}{2}$</td>
</tr>
<tr>
<td>$\frac{1}{Y}$</td>
<td>$\frac{1}{\mu}$</td>
<td>$\frac{1}{\mu} (1 + \frac{\sigma^2}{\mu^2})$</td>
</tr>
<tr>
<td>$\frac{1}{\sqrt{Y}}$</td>
<td>$\frac{1}{\mu^2}$</td>
<td>$\frac{1}{\mu^2} + \frac{2 \sigma^4 + 4 \mu^2 \sigma^2}{(\mu^2 + \sigma^2)^2}$</td>
</tr>
<tr>
<td>$y^2$</td>
<td>$\sqrt{\mu}$</td>
<td>$\sqrt{\mu} (1 - \frac{\sigma^2}{8\mu^2} - \frac{15 \sigma^4}{128 \mu^4})$</td>
</tr>
<tr>
<td>$\log \left( \frac{y-1}{u-y} \right)$</td>
<td>$\frac{Ue^\mu + L}{e^\mu + 1}$</td>
<td>$L + \int_{-\infty}^{\infty} (U - L) \frac{e^\mu}{1 + e^\mu} \varphi(t) dt$</td>
</tr>
</tbody>
</table>

where $x_1$ and $x_2$ are the parameters, and $\varepsilon \sim N(0, \sigma^2)$. The prediction of $y$ given $x_1$ and $x_2$ is expressed in Equation 6.

\[
f(x_1, x_2) = e^{\beta_0 + \beta_1 x_1 + \beta_2 x_2 + 0.5 \sigma^2}. \quad \text{[Eq. 6]}
\]

Note that a bias correction for prediction is employed in Equation 6. Comparing this approach to inversely transforming the prediction of $\log(y)$, the bias correction provides unbiased, or, at least, less biased predictions for the response.

Discussion of this topic can be found in the literature (4, 5). Table II provides the bias-corrected prediction formulas for some commonly used transformation functions.

Also notice that, in Equation 6, the change of predictions contributed by $x_1$ relates to the value of $x_2$. The analytical formula of effect size is expressed in Equation 7,

\[
\text{effect size } (x_1) = e^{\mu} \varphi(1) + e^{-\mu} \varphi(-1) \cdot |e^{\mu} - e^{-\mu}|. \quad \text{[Eq. 7]}
\]

In this case, unlike the situation found in the “main effects” model without transformation, $x_2$ has an impact on the effect size of $x_1$.

To illustrate this, Figures 2(v) and 2(vi) display contour plots from the model $\log_{10}(y)=2+0.5x_1+x_2$ in both transformed and original scales, respectively.

Note that, in the plot of transformed scale, the impact due to $x_1$ does not depend on $x_2$, and the same holds for the impact of $x_2$.

However, in the original scale, the maximum changes clearly occur along the top edge (i.e., the impact of $x_1$ when $x_2=1$) and the right edge (i.e., the impact of $x_2$ when $x_1=1$).

This example shows that, even under the simplest case of
linear model with transformation, the effect size of parameter must be evaluated across the entire design space.

When the model or transformation function is complicated, it would not be feasible to evaluate the effect size manually.

Using an algorithm to calculate parameter effect size

As described in the previous session, the effect size of a parameter can be calculated analytically and programmed with any computational language.

However, when more process parameters are included in models, especially with higher order terms, it becomes more complex to derive the analytical solutions. A generalized, practical computational tool is needed.

A grid-search algorithm was developed to calculate the parameter effect sizes for any parameters in all types of linear models. Using this approach, the number of grid levels is set based on the complexity of the model that is being used.

If the process parameters involved interact in linear fashion with other terms, the number of grid levels can be simply set to two at the boundary of the parameter range.

However, if the parameters are involved in higher order curvature terms, the number of grid levels must be set to much larger than 2 in order to accurately locate the global optimum point.

The pseudo code used for the grid-search algorithm is shown below. Note that, when transformation of a CQA is involved, the effect sizes are calculated based on the predictions in original scale with bias corrections.

A grid-search algorithm for effect sizes

Step 1: List all process parameters in the model: \( x_1, x_2, \ldots, x_k \)

Step 2: Set levels of grid for each of the parameters

For \( i \) in 1 to \( k \)

If \( x_i \) has only linear effects in the model, the number of grids is set to \( n_i = 2 \);

Else if \( x_i \) has curvature effects, the number of grid levels can be set to \( n_i = 10^k \), where \( k \) is the number of parameter having higher order effect (e.g., if \( k = 2 \), \( n_1 = 100 \)). The grid points are selected over the ranges of parameters.

Step 3: Generate a matrix with combinations of grid levels of parameters (1, 2, \ldots, \( k \)) as shown below:

\[
[x_i] = [x_{i1}, x_{i2}, \ldots, x_{in_i}], \quad i = 1, 2, \ldots, k \\
[x] = \text{expand grid } (x_1, x_2, \ldots, x_k)
\]

Step 4: Predict CQA (i.e., \( y \)) from its model fit, \( y = f(x) + \varepsilon \)

\( \hat{y} = \text{predict } f(x)[x] \)

Step 5: Determine the effect size (\( \Delta \)) for each process parameter by finding the maximum change of the predicted CQA caused by the process parameter change when other factors are fixed at their possible levels:

For \( i \) in 1 to \( k \)

For \( j \) in 1 to \( n_i \)

For all \( p = 1, 2, \ldots, k \) & \( p \neq i \)

\( \Delta_{ij} = \text{range}(\hat{y}[x_p] & [x_i] = x_{ij}) \)

\( \Delta_i = \text{max}(\Delta_{ij}) \)

Figure 3 graphically shows how the grid-search algorithm finds the maximum changes in a CQA over the ranges of two process parameters. This CQA has an interaction/quadratic model \( y = b_0 + b_1 x_1 + b_2 x_2 + b_{12} x_1 x_2 + b_{22} x_2^2 \). Notice that, for illustration purposes, the grid levels were set to 5 for each of the two process parameters.

An example with algorithm output

For a moisture-sensitive product, aluminum foil and/or foil packaging plus tablet water-activity controls are needed to ensure that the drug product quality is maintained throughout the desired shelf life. A two-level full factorial design of experiment (DoE) was performed to evaluate the impacts of three film coating process parameters—spray rate, air-flow and exhaust temperature—on tablet water activity through the coating process.

Tablet water activity at the end of coating and water activity at the end of cooling are identified as the critical quality attributes, with a target limit of not more than 0.6.
The statistical models of the attributes are given in the following expression:

\[
\text{End of Coating} = 0.324 + 0.0388 \times \text{Spray Rate} - 0.0138 \times \text{Air Flow} - 0.0338 \times \text{Exhaust Temp}, \ R^2 = 0.9763
\]

\[
\text{End of Cooling} = 0.28 + 0.0225 \times \text{Spray Rate} - 0.0150 \times \text{Air Flow} - 0.0375 \times \text{Exhaust Temp}, \ R^2 = 0.9716
\]

Process parameter criticality was assessed based on Z scores of water activities and parameter effect sizes. Given the calculated average (0.32), the standard deviation (0.058) and the target limit of NMT 0.6, the Z score for water activity at the end of cooling process is 6.38. Because the Z score is greater than 6, all three parameters are considered to be non-critical.

Given the calculated average (0.28), the standard deviation (0.05), and the target limit of NMT 0.6, the Z score for water activity at the end of coating process is 4.80. Because this Z score is in between 2 and 6, additional assessment is required via the 20% rule to quantify individual parameter effect sizes. Figure 4 displays the calculated z-score and the effect sizes by grid search. Because the effect size of spray rate is greater than 20% of QTR, spray rate is designated as a CPP.

### Summary

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Understanding the fluid being conveyed can help maximize the efficiency of your project to assist with easier flushing and avoidance of costly leaks.

Tubing selection
Proper tubing selection, which is detailed in the following section, will ensure that the tubing matches the requirements for the fluid system design. When choosing the right tubing for an application, there are many factors to consider. To make the process simple, use the acronym STAMP—size, temperature, application, media, and pressure—to help remember each factor.

Size. The ID, OD, and wall thickness of the tube are significant factors in pressure and vacuum ratings and must be considered in the decision. The tolerances are also a concern for optimal operation in peristaltic pumps. The typical tolerance of off-the-shelf nominal tubing can be greater than +/-5%. If this non-precision tubing is used, it can cause problems with volumetric accuracy, suction lift, or pressure; poor tubing life can also be a result.

Temperature. Operating temperature is most often considered due to its importance, but cleaning temperature, ambient temperature, and the overall temperature fluctuation must also be considered. Sudden changes or extreme temperatures can negatively affect performance and cause premature failures. A higher cost material has traditionally been the only option to improve performance in extreme temperatures. With advances in manufacturing capabilities, however, multilayer products are available that can help ease this cost while still meeting the performance expectations.

Application. Understanding the full scope of the application is the most complex portion of the selection process and most often overlooked. Regulatory concerns are always at the top of the list. Understanding...
what documentation is needed and what special regulations must be complied with are important; different compliance concerns may call for different material selection. Tubing materials and formulas can be tested to ensure they comply with the appropriate criteria.

Knowing the dynamics (e.g., flow rate, pressure, or viscosity) of the application will assist with material selection for clarity, durometer (relative hardness), flexural fatigue, abrasion resistance, spallation (the tendency of materials to release particulates due to impact or stress), and particulates (pyrogens). There are materials available to combat each of these concerns individually and multi-layer options to solve a mix of these factors.

**Vacuum and positive pressure create stress on any tubing product.**

**Media.** Knowing the media or fluid being transported and its characteristics, such as extractables level, the tendency for adsorption or absorption of fluid into the tubing material, and the tendency of media to entrap particulates, is necessary to assure high purity. Different chemicals attack various materials at different rates, so understanding all the chemicals that might be used in the tubing will help with proper selection. Cleaning agents are often the most aggressive fluids used; be aware of any chemical reactions which might be caused by cleaning or sterilizing agents. Often overlooked are the ambient chemicals (e.g., solvents) present in the atmosphere, either present in the air surrounding the tubing product or dripping by way of leaks or condensation creation. The effect of these chemicals on the tubing should also be considered. If the fluid is very aggressive, a more resistant material can be used, or multilayer tubing can be selected that assists with barrier protection but is not as costly as tubing made completely from a more resistant material.

Some tubing materials can be produced at tighter tolerances for tighter fitting connections to avoid leak points. Others can be produced with a smoother inner surface for better flushing. Understanding the fluid being conveyed can help maximize the efficiency of your project to assist with easier flushing and avoidance of costly leaks.

Safety also plays a role with material choice. Some requirements mandate viewing the fluid being conveyed. This means the material must have a sufficient level of clarity to see the fluid path and distinguish if any particulates are present. Other options require identifying marks for various chemicals through the use of colored tubing products or specific marking text. Use of these marks is a growing trend in efforts to further company’s safety improvements.

**Pressure.** Vacuum and positive pressure create stress on any tubing product. Ignoring these factors can create hazardous conditions during product use. Use temperature also has a significant effect on the pressure rating for materials, and proper measures must be taken. Changing the wall thickness can help increase pressure rating, as can reducing the overall OD and ID. If these measures are not an option, multilayer products of various materials can help handle the desired pressure as well as maintain the proper condition in the fluid path.

Pressures created during normal operation are not the only factor when selecting the proper tubing. Cleaning or sterilization cycles can create the most extreme pressure conditions and must be considered during the selection.

**Summary**
The peristaltic pump system can be optimized with proper tubing installation material selection that takes into account the size of the tubing and the temperature, application, media, and pressure of the system. When selecting a tubing product, quality is of the utmost importance. Do not shy away from asking the manufacturer about their quality process, and take a plant tour to see how a product is designed and produced. Should something ever go wrong in the field, a manufacturer should have the supporting quality documentation.

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Figure 1. Stretch tubing slightly while loading it into the peristaltic pump, and make sure it is in the centre of the roller and occlusion bed.
Determination of Dermal PDE for Pharmaceutical Products

The authors offer recommendations for permissible daily exposures and concentration limits of elemental impurities for dermal drug products.

The International Council for Harmonization Guideline for Elemental Impurities (ICH Q3D) establishes permissible daily exposures (PDE) in μg/day to evaluate elemental impurities (EI) in pharmaceutical drug products (DP) administered by oral, inhalation, or parenteral routes. The guidance document provides the option to re-evaluate PDEs for alternative administration routes when supported by data, taking into consideration specific toxic endpoints by other routes and differences in absorption. Differences in absorption between the dermal and oral routes are known for several compounds (1); thus, dermal absorption data may allow re-evaluations (increase or decrease) of some oral PDEs.

On the other hand, as the skin is the primary organ in contact with DP, specific toxic endpoints may appear for some EIs and require a specific dermal PDE (dPDE). Among skin-specific toxic end points, sensitization has been identified for few EIs after dermal contact from occupational exposure or from cosmetic and house-hold product uses (2–4). Such exposure represents an additional safety issue to consider in the evaluation of EIs in dermal DP.

The authors conducted an analysis of all EIs for which an oral PDE was assigned in ICH Q3D to identify differences between oral and dermal bioavailabilities, following the work previously published by Tesdale et al. (5). When possible, the oral PDE was corrected by the difference between the oral and dermal absorptions to propose a specific dPDE for topical DP. In addition, skin sensitization was investigated to propose minimal dermal concentration limits (μg/g) for few EIs in DP.

Sufficient data to correct the oral PDE were available for a few EIs only, but establishing a dPDE may increase the safety of dermatological products. Skin sensitization has been identified as a cause of potential safety issue for a few EIs. The consideration of concentration limits, in addition to PDEs, may increase the safety of EIs for their overall dermal safety evaluation.

Study methods

Safety evaluation. For each EI, a literature search for toxicity endpoints was performed covering the time period since the establishment of the oral PDE for the EI. New information related to carcinogenicity, genotoxicity, reproduction toxicity, and dermal toxicity—including sensitization—were particularly scrutinized.

Determination of oral and dermal absorptions. The literature search explored the oral absorption value for each EI when administered under its specific ionic salt form corresponding to the no observable adverse effect level (NOAEL) in animal studies, or to the maximal residual limit (MLR) in humans; this information was used to calculate its oral PDE. When ranges of values were reported without a definitive conclusion, the lowest reported value—the most conservative approach—was used for the oral bioavailability.

The literature search also explored the human dermal bioavailability for each EI. If no human data were available, in-vitro human skin penetration studies were considered and, lastly, animal data. All ionic forms were generally considered and the most reasonable penetration value was retained excluding maximizing procedures (e.g., occlusion). For chromium (Cr), only Cr(III) was considered; Cr(VI) is highly unstable and reactive, and is unlikely to be present in DP.

The percentage of dermal penetration was calculated as the sum of quantities recovered in the stratum corneum, epidermis, dermis, and in the liquid receptor. Skin washing procedures or tape stripping before measuring skin concentrations were considered on a case-by-case analysis. When in-vitro dermal applications were conducted for more than 24 hours, results were interpreted with caution.

Calculation of dermal PDE. When oral bioavailability data to establish the oral PDE and human skin dermal penetration were both available with a certain level of robustness from literature, the ratio of the oral values versus the dermal values were calculated. The dPDE was then calculated by multiplying the oral PDE by this factor if dermal and oral absorptions differed by at least a two-fold factor.
Determination of concentration limits. For each EI, a review of the dermal toxicity was undertaken, looking for specific dermal toxicity, dermal irritation, and skin sensitization. When a particular safety endpoint was identified by the dermal route (toxicity or sensitization), the minimal concentration at which such effect is not expected to occur in the normal population was proposed as the dermal concentration limit. For skin sensitization, the dermal concentration limits selected were from subjects not previously sensitized for the EI and were based on human studies conducted under normal conditions, excluding concomitant uses of irritants (e.g., sodium lauryl sulfate) and occlusive patch applications exceeding 24 hours.

Results
Due to missing data for oral or dermal absorption, it was not possible to determine dPDE for antimony, barium, gold, iridium, molybdenum, osmium, palladium, rhodium, ruthenium, selenium, thallium, tin, or vanadium. A summary of results for other elements can be found in Table I.

Discussion
Among the 24 elements in the ICH Q3D guideline evaluated for dermal absorption, PDEs were unchanged for 21 elements, increased for one and decreased for two. The literature search found that absorption data was not available for at least one route of exposure for antimony, barium, gold, iridium, molybdenum, osmium, palladium, rhodium, ruthenium, tellurium, tin, selenium, and vanadium. Oral and dermal absorption values were within the same range.
Elemental Impurities and concentration limits. Ni is nickel. Hg is mercury. Co is cobalt. Cr is chromium.

For Hg, Co, Ni, and Cr, compare above EI concentration limit with dermal concentration limit.

For Hg, Co, Ni, and Cr, compare above EI concentration limit with dermal concentration limit.

Apply lower limit.

Example: The dermal PDE for Ni is 110 μg/day; thus, the daily exposure from a dermatological DP should not exceed 30% of it (e.g., 33 μg/day). As the concentration limit for Ni is 5 μg/g—up to a quantity of 6.6 g/day of DP (33/5)—the concentration limit of 5 μg/g will be the applicable limit. Above 6.6 g/day, the 30% of the PDE (33 μg/day) will be the applicable limit to determine the maximal concentration of Ni in the dermal DP; (33 μg/day divided by the daily quantity of DP); this corresponds to a concentration of 3.3 μg/g for a DP applied at 10 g/day.

These concentration limits will increase safety by limiting high concentrations of products on small skin areas, which could cause skin sensitization elicitation or reactions.

The dermal concentration limits defined apply only for compounds applied on the skin without rinsing. In case of restricted uses (e.g., shampoo), mitigation factors taking into account the time of contact may be applied as described in cosmetic regulations (6). For example, for a shampoo, a retention factor of 0.01 can be applied, increasing both the concentration limit and the PDE. Evaluation of such short-contact DP should be made on a case-by-case basis.

These concentration limits must not be applied for DP applied as occlusive patches as it is well recognized that occlusion increases significantly the risk of skin sensitization reaction or elicitation (7). In addition, uses of occlusive patches compromises the skin function barrier and often increase percutaneous absorption. Thus, for drugs applied with occlusive patches, the skin penetration should be measured. If the change in dermal absorption is greater than a two-fold factor, the concentration limit and the dermal PDE should be corrected, or a dPDE should be established from the oral PDE.

Finally, these dermal concentration limits and revised PDE are not applicable for topical DP applied on skin requiring preparations, like curetage, keratolytic pretreatment, or abrasion, for which a case-by-case evaluation should be performed, taking into account changes in dermal penetration.

In conclusion, the authors propose the establishment of dPDEs for some EIs to take into consideration differences between oral and dermal penetration levels and to set dermal concentration limits for some EIs due to their significant skin sensitization risk. These new values should ensure a higher safety profile of dermal DPs.

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References
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The Industrial Internet of Things (IIoT) involves connecting “things” (i.e., equipment) through the Internet. “Smart” equipment uses sensors to provide data for improving a process or monitoring equipment health, for example.

“The IIoT brings new options to the table for collecting data from the process and sending it to manufacturing execution systems and distributed control systems (DCS),” explains Greg Newman, vice-president of Marketing at Parsec Automation Corp. “IIoT devices on the plant floor are being used to reduce the investment in infrastructure and setup time for simple data collection tasks, such as production counters, temperature measurement, and equipment state. IIoT devices can also more easily enable sending these data off-site to remote data-capture software.”

Predictive maintenance

Manufacturing companies from different industries are relying on data analytics, with data collected by the IIoT, to solve problems related to unscheduled downtime, a survey conducted in 2016 by Honeywell found (1). Although pharma manufacturing is different from other manufacturing sectors in its focus on regulatory compliance and in the types of equipment being used, the ultimate aim to prevent downtime and improve reliability still applies. “Manufacturers want to produce high quality products, and they don’t want to lose batches. Monitoring equipment and process data is crucial to achieve this goal,” notes Matthias Maaz, director of Pharma and Specialty Chemicals, Honeywell Process Solution.

“Predictive maintenance might be the killer app for IIoT,” says Petter Mörée, industry principal for Life Science, Food and Beverage, Chemical at software supplier OSIsoft. Mörée reports that one pharma company using remote monitoring of real-time data had reduced unplanned downtime at a facility because it could more closely monitor conditions such as temperature and humidity, and calibrate systems more accurately.

“Continuously collecting real-time data from the operating equipment and machines, and then analyzing these data to harness and deliver actionable insights related to asset utilization will help with failure prediction and can improve uptime in all the machines across the plant,” says Billy Sisk, Life Sciences Industry manager for EMEA at Rockwell Automation. He says that although predictive maintenance isn’t a new concept, more data can now be captured, and the cost of computing and data storage is now lower. “One of the key values of scalable analytics is the ability to leverage all the data gathered from the shop-floor equipment and analyze it to improve plant and asset performance. For instance, pharmaceutical producers can monitor performance at an equipment or system level, and track what assets are failing more frequently or are degrading. This information can be used to develop a comprehensive maintenance and predictive asset-management programme.”

Troubleshooting is also enhanced. For example, reports Sisk, a biopharmaceutical company that was upgrading to new purification skids added monitoring of the skids’ variable frequency drives (VFDs). “The VFD fault codes are reported to the programmable logic controller (PLC) and collected in a data historian. The company said using such monitoring saved a day’s worth of troubleshooting in just the first week. The new skids also support workers who want remote access from the office or another location, which provides the ability to begin troubleshooting in mere minutes.”

Another example of an IIoT-enabled device is the i-ALERT2 Bluetooth Smart monitor from ITT. The monitor tracks pump vibration, temperature, and run-time hours, and the data are sent wirelessly to cloud storage for analysis of equipment health. Guidance can then be sent to the operators to schedule regular maintenance, and the system can alert operators of problems so they can take action to prevent equipment failure.

Process optimization

Equipment performance is directly affected by process performance, and overall production reliability is
Intertwined with overall equipment effectiveness (OEE), says Edwin van Dijk, vice-president of Marketing at TrendMiner, a company offering self-service industrial analytics software. "With the IIoT, you can connect a piece of mobile equipment and the system automatically identifies the equipment and knows information such as its cleanliness status. The IIoT simplifies configuration and prevents connection errors."

"The IIoT can optimize manufacturing processes that use single-use equipment, which require equipment tracking, flow-path verification, material tracking, and hygienic status tracking," says Sisk. In the facility of the future, he envisions that "workers will move assets such as mobile mixing tanks and smart totes into and out of production areas. A modern DCS can coordinate this movement, including verifying the right asset is in the right place, executing production processes, releasing equipment modules, and disabling display information after a process is complete. Mobile tablets or screens on wheels will be able to go with operators as they follow production from one process area to another."

### Remote monitoring

The IIoT is built around sending data from the plant floor to "remote" locations, whether these locations are a few feet away in the facility control room or many miles away at a location where specialists can analyze the data. Pharma manufacturers are typically leery of the concept of remote monitoring, says Maaz, because they don’t want equipment manufacturers to have direct access to their DCS and to sensitive data. "Remote," however, could also mean that a pharma manufacturer’s engineers have a secured line of information from the process at their desktop or mobile device, or that the maintenance person outside of the cleanroom can have access to data at the same time as the operator inside of the cleanroom, explains Maaz. "The 'mobile operator' can be in the area but not directly at the equipment monitor. They can carry a mobile human-machine interface (HMI) that can alert them when a disturbance may have occurred,” he adds.

"Decision making in pharma manufacturing is not just by the operator," says Maaz. "The operator, quality assurance personnel, management, and regulatory compliance personnel also want access to data. An IIoT platform is flexible and enables everyone to be involved in complex decisions."

In addition to data access, data configuration is important. For the operators, for example, the HMI should present information “in a way that they can use it, so they can react to a disturbance, for example, or be reminded what process step is coming up next so they can prepare for it,” explains Maaz.

It can also be valuable for remote access to be given to an equipment manufacturer to look at a specific issue. This access, which could be enabled and then disabled again, would be limited to specific instances under high security, adds Morse.

Another potential use of remote monitoring is that pharma companies may be able to use IIoT technology to remotely monitor and track production at a contract manufacturing organization, enabling them to ensure data integrity and optimize production at different sites, says Mörée.

### Security challenges

Securing IIoT devices is a significant concern. "There are many facets, including isolating the interference that a rough data collection device could cause, to the overall network exposure as the devices are opened up to the public internet," notes Newman.

Contin. on page 45
When it comes to outsourcing process validation of biologics, Abel Hastings, director of process sciences at FUJIFILM Diosynth Biotechnologies, says that the relationship between a contract development and manufacturing organization (CDMO) and sponsor is key in ensuring successful process validation. “Customers that are open about their strategy, their data (good and bad), and their own strengths and weaknesses are most successful.”

Pharmaceutical Technology Europe spoke with Hastings about the specific challenges that arise in the process validation of biologics.

Challenges specific to biologics

PTE: What are the challenges of performing process validation during Phase III of biologics development?

Hastings: A primary challenge we see is viewing validation as phase-specific. Ideally, process validation should be an extension of the development and refinement processes. To support this, develop a long-term strategy for implementing some of the validation-readiness tools in simple versions early in development so that a transition toward validation is less a change in course and more an acceleration of the project.

PTE: What aspects of process validation should companies focus on when preparing to submit a biologics license application to FDA?

Hastings: As a CDMO, FUJIFILM Diosynth Biotechnologies has seen quite a variety of validation strategies. Some strategies are influenced by indication, regulatory designation, or client platform. Some common themes have shown themselves to aid in success of many of these projects. These themes include building clear attribute-parameter linkages, taking a systematic approach to validation, and leveraging data-driven risk management.

Clear attribute-parameter linkage begins with a fundamental understanding of the molecule attributes, the measurement systems, and the potential points of variation and ambiguity therein. This knowledge of the measurement can then be applied to the process control strategy including any ambiguity and interaction with other attributes. A team’s focus on required control becomes increasingly clear by applying a logically mapped linkage from attribute to the controlling parameters.

“...building an iterative and logical risk-management programme that is based on data-driven decisions.”

—Hastings, FUJIFILM Diosynth Biotechnologies

A systematic approach to validation that is based on consensus on both definitions and readiness criteria and is aimed at long-term commercial execution is recommended. We have refined our validation-readiness process to achieve a balance between lean efficiency and sustainability. This development required careful attention to details such as definition subtleties, systematic documentation linkage, quantitative assessment including leveraging previous data, and systematic manufacturing execution standards. This focus on mechanistically applying pre-built tools has proven to be successful with numerous clients efficiently driving their projects to success.

We also recommend building an iterative and logical risk-management programme that is based on data-driven decisions. As progress continues toward validation, teams can often be influenced by process history (both recent and past), which can lead to decision making with unintended consequences. We push teams to iteratively refine risk-management documents when new data come available thereby allowing them to make decisions based on data, even in the ‘heat of the moment.’ To guide teams, we have built a series of risk-management tools that range from simple and focused on one problem to large and involved FMEA [failure mode and effects analysis]. This focus on regularly reviewing and documenting risk and data evolution has expedited project execution in a reliable manner.

PTE: What protocols or tools are used in process validation of biologics compared with solid-dosage drugs?
Hastings: Biologics, when compared with solid-dosage product, can be a sea of parameters and attributes, many with a high degree of variability. We have a systematic approach to process validation that draws on experience from more than 300 molecules; this allows us to focus attention on what matters most. We first begin with high-level process mapping intended to focus attention on parameter-attribute pairings. The next step, which includes smart use of a proprietary FMEA-like software tool, can help focus characterization and equipment adjustments to help improve process reliability. Finally, our platform quantitative assessment tool for parameter-attribute pairs confirms readiness for process validation. Taking this systematic approach, we have been successful in cutting through a large number of variables to reduce variation and ensure right-first-time success for validation campaigns with tight timelines.

Utilizing process validation data

**PTE:** How can the data obtained during process validation be used elsewhere in the production cycle?

**Hastings:** Process validation should be designed to demonstrate the capability of the process to support commercial manufacturing. To this end, the data generated during process validation should be the forerunner to the commercial control charts. A primary question when reviewing an initial set of commercial data should be: how do these data compare with the expected variation from my validation-preparation activities? Ideally, we expect commercial manufacturing to flow seamlessly from validation, but due to the artificial-perfection that can accompany validation, some changes are expected. Recognizing these subtle changes, and mitigating them as early as possible, can substantially improve long-term manufacturing reliability.

“Process validation should be designed to demonstrate the capability of the process to support commercial manufacturing.”

—Hastings, FUJIFILM Diosynth Biotechnologies

Supply chain considerations

**PTE:** How can process validation help companies ensure their biologic’s supply chain is reliable?

**Hastings:** Process validation is not just about three batches in a row. It is about launching a reliable commercial process. This is why we design process validation campaigns around an expectation that sustained commercial supply must be planned for.

The quantitative pre-validation statistical guidelines and systematic tool-sets we use for validation-readiness have been developed and built around the expectations that projects must have data to support sustainable commercial success. Approaching statistical risk management with more pre-validation runs is a common practice for many companies, but our [process validation] philosophy extends beyond that to leverage a large body of pre-existing data and rigorous process-agnostic testing to augment process-specific data. To our clients, this means improved knowledge of their supply chain expectations prior to process validation. **PTE**

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**Internet of Things — contin. from page 43**

Although the ability for remotely located software solutions, either in the cloud or in central private data centres, is a significant potential benefit for pharma manufacturing, the biggest barriers to using such solutions, Newman says, are “reliable remote connections and network infrastructure, as well as organizational maturity in setting up risk-acceptable security around the implementations.”

Additional connections can create more potential entrance points for threats, adds Sisk. “Pharma producers should adopt a defense-in-depth security approach, which deploys multiple layers of protection, assuming that any one protection point can and likely will be defeated. Some security measures that pharma producers should use as part of a defense-in-depth strategy include anomaly-detection software, AAA [authentication, authorization, and accounting] software, and an industrial ‘demilitarized zone.’”

A survey sponsored by Honeywell found that industrial companies, in general, are lacking in their adoption of cyber-security measures. “To take advantage of the tremendous benefits of industrial digital transformation and IIoT, companies must improve their cyber-security defenses and adapt to the heightened threat landscape now,” said Jeff Zindel, vice-president and general manager, Honeywell Industrial Cyber Security, in a press release (2).”

**References**


**ADDITIONAL READING**

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- **Using the Internet of Things to Manage Manufacturing Equipment**

- **Real-Time Logistics**
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- **The Internet of Things for Pharmaceutical Manufacturing**

- **Integrating Industrial Internet of Things and Pharmaceutical Manufacturing Processes**
For more than a decade, the bio/pharmaceutical industry has struggled to establish a true electronic pedigree that would allow its products to be traced and verified at any point along the supply chain. The European Union’s False Medicines Directive and the US Drug Supply Chain Security Act (DSCSA) set timelines and requirements for serializing product packaging, aggregating product and lot-level transaction data electronically, and sharing information with distributors and at the point of use or sale.

Even though serialization is only the first leg of the journey toward full traceability, the technical challenges and costs are significant. This is due to a “fundamental mismatch of applied integration technologies for inter-plant, plant-to-enterprise, and distribution repack exchanges,” says Charlie Gifford, technical director of the Open-SCS Packaging Serialization (OPEN-SCS) Working Group.

In addition, he says, distinct data elements required for serialization and traceability are interrelated. Examples include workflow rules; serial number formats; data sets (i.e., those established by regulators vs. those used by vendors vs. those for users); provisioning and serialization events; master data and associated technologies (e.g., for production, ordering, and reporting) so the data and their relationships must be agreed upon and specified for data accuracy and exchange interoperability. Understanding and agreeing on data relationships across the overall serialization process is extremely challenging, Gifford says.

Open standards
Four large life-sciences companies and five solution providers established the OPEN-SCS working group in February 2015 to sort through these issues. Their goal was to stem pharmaceutical counterfeits by developing open, vendor-neutral data-exchange solutions that would simplify integration of the components and systems required for product serialization and traceability.

The group now has more than 25 active members and 100 interested supporters. OPEN-SCS achieved a number of important goals in 2017 (see Sidebar), establishing a collaborative agreement with the International Society for Pharmaceutical Engineering (ISPE) and approving the first version of the Open-SCS Packaging Serialization Specification (PSS 1.0).

Plans call for OPEN-SCS to release Good Automated Manufacturing Practices (GAMP)-compliant user requirement specifications (URS), functional specifications (FS), and operational and installation qualification (OQ/IQ) templates in March 2018. A core group of vendors (ACG Inspection Systems, Advanco, Antares Vision, Arvato Systems, Optel Vision, Systech, TraceLink, Tradeticity, Uhlmann, Vantage Consulting, and Wipotec-OCS) is developing interfaces for one or more of the four use cases of PSS 1.0, says Gifford. Each vendor may commercialize compliant interfaces by the end of the third quarter of 2018.

Efforts are underway to reduce the cost and time required for serialization projects and their underlying data integration.

The group expects these efforts to reduce the cost and time required to implement serialization and traceability projects by at least 50% when applied across multiple packaging plants. "For most companies today, integration typically means custom projects," says Evren Ozkaya, founder and CEO of Supply Chain Wizard. "OPEN-SCS will improve the standardization of exchanged data and their data structure in communications between plants, and between plant and enterprise systems, which will reduce cost."

Addressing the readiness gap
Reducing complexity and cost will be crucial to advancing traceability initiatives within smaller companies, especially generic-drug manufacturers and smaller contract manufacturing organizations (CMOs), whose margins are extremely tight. “These companies don’t typically see any direct benefits by investing in expensive systems that track their products throughout the supply chain,” says Marcel de Grutter, OPEN0SCS executive director. "Even
Moving toward open serialization standards

It was a busy year for the Open-SCS working group. Charlie Gifford, technical director of the group, summarized developments that occurred in 2017.

**PTE:** How did you decide to use good automated manufacturing principles (GAMP) lifecycle best practices for the serialization standards?

**Gifford:** The User Requirement Specification (URS) and Functional Specification (FS) for the standard Packaging Serialization Specification (PSS) version 1.0 were approved by the members in August. Three member companies are already using them as templates for projects, and providing feedback for ongoing validation testing.

However, in June, we took the International Society for Pharmaceutical Engineering’s (ISPE’s) recommendation and adopted the GAMP lifecycle best practice of conducting a full validation test and report using prototype OPC-UA prototype interfaces in order to refine PSS 1.0’s URS, FS, and operational and installation qualification (OQ/IQ) templates. The new PSS 1.0 package is set for formal release in March 2018, depending on available member resources. Eleven vendor members have committed a developer to build prototype interfaces for the validation test. This design-build-test exercise has already brought out many functional requirements that had not been addressed in the previously approved draft.

In December, work began on a PSS 2.0 URS working draft, which is scheduled for member review in February. Six inter-plant solution providers are working on this project. Depending on availability of member expert resources in 2018, we hope to accelerate and release PSS 2.0 by the fourth quarter of 2018.

**PTE:** What kind of participation are you seeing among pharma companies and contract manufacturing organizations (CMOs)?

**Gifford:** Membership is now over 25, with 100 interested companies saying that they will join the group, either when PSS 1.0 is released addressing plant operations (Level 3) to enterprise (Level 4) exchange use cases for regulation reporting, or once the PSS 2.0 addresses Level 2-to-Level-3 exchange use cases.

**PTE:** What have been the most challenging technical aspects of developing this standard? How are they being resolved?

**Gifford:** One major challenge was dealing with the high-level complexity of the packaging serialization scope and problem data (product, order, reporting) and their associated integration technologies. As we’ve learned after working on these problems for the past 28 months, the root of the problem often lies with pharma customer requirements. Most pharmaceutical manufacturers’ serialization exchange requirements force their vendors to customize GST1’s EPCIS schema into forms that are not interoperable, that don’t scale, and that do not apply the required transaction methods. GST1’s EPCIS experts have worked directly with our team to ensure that the PPS 1.0 [specifications for each use case] comply with GST1 or at least are as closely aligned as the scope of the given project permits.

Because EPCIS does not address serial number management and inter-plant packaging serialization workflows, another major challenge was developing a Serialized Identifier (SID) event lifecycle model for the events, states, and transition for serial number management and serialization events between the packaging plant and enterprise. Along the way, we’ve had to respond to the challenge that any new collaborative organization faces: how to fund all this work. We are still working to find the best business model that will support new projects and updates from changed and new regulations.

**PTE:** How difficult has it been to establish consensus among members from such different groups?

**Gifford:** It was especially challenging during 2015 and 2016, when there was a great deal of debate on whether PSS 1.0 should address data exchange between the site serialization manager-actor (Level 3) and the enterprise serialization manager-actor (Level 4) or between the packaging line serialization manager-actors at Levels 2 and 3. We held four workshops on this topic alone during that period.

**PTE:** How difficult is it to get the high-level IT help that this work demands?

**Gifford:** Hiring skilled developers, for the funding that is available, is a challenge for all manufacturing and business sectors, especially as Manufacturing 4.0 initiatives take shape, and the difficulties that we are seeing now are only the beginning. Finding developers would be difficult enough, but integration-specific developers are a rare breed. They need to have over five years of experience and mentoring in order to be competent enough not to compromise data accuracy and security.

This challenge has dramatically affected the ‘quality’ of the serialization solutions deployed in the life sciences industry. Having a standardized approach will significantly reduce risks. At this point, though, life-sciences companies are not openly acknowledging and reacting to the supply of talent. For example, the ongoing hourly pay rate for developers with the necessary skills has increased to $US 180—200 per hour. Pharma companies are paying them $US 80—120 per hour, so many developers in life sciences get additional training and leave the sector for better-paying jobs elsewhere.

**PTE:** What has made you most proud of OPEN-SCS’ achievements so far?

**Gifford:** First, it’s important to recognize that the top solution providers, which compete against each other on a daily basis, are working together on this project and exchanging proprietary know-how in order to reach a common result. These efforts have all been driven by the desire to benefit patients by reducing deployment timeframes and the cost of ownership, while ensuring data integrity.

It has also been gratifying to see the contributions of experts from GST1, ISPE, the OPC Foundation, and solutions providers align in these efforts.

On the technical side, the working group made some significant progress in developing the Serialized Identifier (SID) Lifecycle Model and the Packaging Order and Product master data use cases and their supporting interfaces.

**PTE:** What have you learned from the pilot tests?

**Gifford:** We achieved a number of benefits by using OPC Universal Architecture (UA), which allowed us to find and fix holes in the original draft standards. We used UA to develop the validation test, FS, and associated OQ and IQ modules. The validation tests have provided a foundation for certification programmes, and, as previously mentioned, solutions providers are participating in the validation test by developing interfaces.

**PTE:** What are you planning for the next phase of this work?

**Gifford:** We began working on a draft of the PSS 2.0 URS in December for review by members in February or March. The approved scope of this standard specification will extend use cases for serial number provisioning and return as well as serialization master data, and event reporting. It will also address use cases for rework and multistep processing. Version 2.0 will also incorporate new use cases determined through customer surveys and an April 2017 workshop, including serial number provisioning for lot start; end-of-lot issues such as unused serial number returns and unused, decommissioned, orphaned, or sampled serial numbers; end-of-lot issues with full batch data and mid-lot runs; production order downloads for new and rework orders, including aggregation hierarchies; and handling exceptions.
major multinationals struggle with the fact that they are developing fewer blockbusters so they are continuously restructuring, to support their commercial products” he says. As a result, implementations are being delayed, as serialization competes with more pressing priorities, such as ensuring a continuous supply of product, he says. In 2017, after realizing that many smaller companies had not even begun serialization efforts, US Food and Drug Administration (FDA) officials extended DSCSA’s original serialization enforcement deadline by one year, to November 2018 (1).

Still, a readiness gap remains. Most large pharma companies are ready, or were a while ago, but some companies still haven’t begun formal serialization programmes, while others that see themselves as ready have only serialized part of their packaging lines, says Ozkaya (see Sidebar). For those manufacturers “their most painful days are ahead of them,” he says, because serialization efforts tend to lower productivity and line efficiency during the early stages of implantation.

The number one issue, for contract companies and their clients, is CMO readiness, says Ozkaya. “FDA’s enforcement delay was a welcome move for the industry, but companies need to speed up implementations by staffing their project teams properly, partnering more closely with their solution providers, and proactively managing both their internal site and external CMO compliance risks,” says Ozkaya.

Observers see industry mindset as part of the problem. Until recently, most pharma company leaders viewed serialization as a compliance need, with no return on investment, says Gifford. At a time when more countries around the world are setting serialization requirements, regulators often underestimate what it takes for any company to implement a full track-and-trace system. “Changing requirements and timelines do not help,” he says.

### Exploring value beyond compliance

Even though basic compliance issues remain unresolved, more companies are starting to explore ways in which their efforts and investments in serialization can be leveraged to improve overall operations. One common focus is to improve overall equipment effectiveness (OEE) in packaging, to offset decreases in efficiency that are seen in early implementation stages. “Some companies have assigned dedicated leaders to work on this, while others have invested in finding business use cases to extract value from serialization data and their ecosystem,” says Ozkaya.

Instead of keeping these efforts to themselves, more companies are talking about what they are doing at industry conferences, and conducting internal pilot projects and collaboration initiatives with their trade partners to create long-term strategies. “A few years ago, we were trying to convince companies to look into supply chain and operational improvements in the serialized world. Today, more companies are taking the initiative and reaching out for help, which is a positive sign,” Ozkaya says. “The industry is moving in the right direction, even though its serialization and traceability initiatives may still lack speed and momentum,” he says.

### References


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**Surveys redefine “ready”**

In December 2017, TraceLink released findings from a survey of 660 serialization partners, including 174 pharmaceutical companies and 155 contract manufacturing organizations (CMOs) (1). Results, due to be published during the first quarter of 2018, suggest that only one third of the pharma company and CMO executives surveyed see their companies as being “very ready” for the US Drug Supply Chain Security Act (DSCSA) serialization deadline in November 2018.

Most of the companies who feel well prepared had taken many of the necessary steps, but there were some notable gaps. For example, only 8% had integrated efforts with most (i.e., 81–100%) of their CMOs. Only 11% reported that 81–100% of their CMOs were ready to ship serialized product, while only 12% reported that internal packaging line equipment had been ordered and fully installed, and that 81–100% of their internal packaging lines were ready. In addition, 23% were not concerned about equipment and skills shortages affecting serialization compliance, and only 37% had moved away from paper-based lot transaction records. Half of CMOs surveyed felt very ready for DSCSA, but only 23% reported that they are integrated with their pharma customers, while 22% say brand owners are ready for integration. Only 9% are concerned about equipment shortages having an impact on compliance. For pharma companies and CMOs, only one third reported feeling “very ready” for the EU’s Falsified Medicines Directive (FMD).

An earlier 2017 survey (2) by the Healthcare Distributors Association examined the industry’s readiness for serialization based on responses from professionals from 67 manufacturers, including 15 of the top 20 based on product sales. This survey also found readiness gaps, with 3% of generics and 34% of branded-product manufacturers expecting to ship 100% serialized product to distributors by November 2017. By November 2018, however, 69% of generics and 91% of branded pharma companies are expected to do so.

By November 2017, 24% expected to send serialized data to distributors, but 33% said they will send it by November 2018 and 30% expect to send it between 2018 and 2023. However, 13% are unsure that they will send serialized data.

References


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Danapak Flexibles A/S

Company description
Danapak Flexibles A/S, a subsidiary of Schur Flexibles, has 40 years of experience supplying flexible packaging laminates to the pharmaceutical industry. It all began supplying high barrier laminates to the transdermal therapeutic industry, and later on-the-wound and dressing industries were served. In recent years, new product developments for blister packs, stick packs, peel sachet as well as anticounterfeit solutions have been introduced.

Major products/services being exhibited
Apart from the well-known range of laminates for the transdermal, wound and dressing industries, a range of completely new developments will be presented:

a. A new patent pending push-through blister lidding material comprising of a paper/alu/coex seal layer. This specification replaces traditional 20μ alu/lacquer solutions offering broad sealing windows to all common bottom web materials such as PVC, PVdC, PET and PP. The paper surface offers excellent printing options, but most importantly this new specification offers significant sustainable advantages as the alu content is reduced by more than 65% and the overall weight is reduced by 10% compared to traditional 20μ alu specifications.

b. A range of paper/alu/polymer laminates for stick-packs for dry and liquid products offering easy tearing of the packs through use of polymer seal layer instead of traditional sealing films. This range also is distinguished by excellent printing options through the use of high quality paper.

c. A cost effective series of paper/alu/ co-ex peel polymer laminates for sachets offering constant and smooth peel opening of the sachets through use of coe-ex polymer technology. The laminates are also feature excellent barrier properties and are mainly used for solid and dry products.

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Booth M40

Catalent Pharma Solutions

Company description
Catalent Pharma Solutions is the leading global provider of advanced delivery technologies and development solutions for drugs, biologics and consumer health products.

With over 80 years’ experience across prescription and consumer markets, Catalent has the deepest expertise, the broadest offerings, and the most innovative technologies to help its customers get more molecules to market faster, enhance product performance, and provide superior, reliable manufacturing and packaging results.

From a single, tailored solution, to multiple answers throughout a product’s lifecycle, Catalent can improve total value of treatments and accelerate programmes to clinic and beyond.


Major products/services being exhibited
Catalent’s prefilled syringes provide safety and convenience advantages over multi-dose forms.

From its European and U.S. sites, Catalent provides specialized scientific support and manufacturing of complex injectable treatments. As a leader in sterile manufacturing, Catalent offers a customisable range of prefilled syringe products, innovative fill-finish processes, and speciality delivery vehicles including auto-injectors.

Catalent recently acquired Indiana-based Cook Pharmica, an integrated provider with extensive biomanufacturing capacity and expertise in sterile formulation and fill-finish across liquid and lyophilised vials, pre-filled syringes and cartridges, augmenting Catalent’s capabilities in cell line engineering, bioconjugate development, analytical services, bio-manufacturing, prefilled syringe, and blow/fill/seal technologies.

Catalent now has an annual syringe-filling capacity of more than 300 million units, and provides access to specialized technologies that ensure extreme precision for safer, more accurate dosing. Its expertise in process design, scale-up, quality assurance, validation and regulatory support provides efficiency and support across virtually any sterile dosage form.

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Hall 7.1, Booth F62
Gerresheimer

Company description
Gerresheimer is a leading global partner to the pharma and healthcare industries. The company’s special glass and plastic products contribute to health and well-being. Gerresheimer is a global organization with 10,000 employees and manufacturing operations in the local markets, close to customers. It has more than 40 production facilities in Europe, North and South America, and Asia generating revenue in excess of EUR 1.4 billion. The comprehensive product portfolio includes pharmaceutical packaging products as well as convenient and safe drug-delivery systems such as insulin pens, inhalers, prefilled syringes, vials, ampoules, bottles, and containers for liquid and solid pharmaceuticals with closure and safety systems, plus cosmetic packaging products.

Major products/services being exhibited
With their exposed cannulas, used syringes are a source of risk at physicians’ surgeries, laboratories, and hospitals the world over. Although existing needle protection systems reduce the risk of injury for the end user, they are more complex for pharma companies to fill and must be handled by medical specialists. With the Gx InnoSafe, Gerresheimer is now offering a syringe with an integrated passive safety system that avoids inadvertent needlestick injuries, prevents repeated use, and is designed with pharmaceutical companies’ production processes in mind as well as being optimized for simple and intuitive use by medical specialists.

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Booth A24

SCHOTT Pharmaceutical Systems

Company description
SCHOTT is one of the world’s leading suppliers of parenteral packaging for the pharmaceutical industry. More than 600 production lines in 13 countries worldwide produce more than 10 billion syringes, vials, ampoules, cartridges, and special articles of tubing glass or polymer. The company has more than 130 years of expertise.

Major products/services being exhibited
iQ™. The Global RTU Standard. SCHOTT’s new iQ™ platform standardizes ready-to-use syringes, vials and cartridges within one tub format. Pharma manufacturers can thus fill various drug/container configurations on the same line and reduce changeover times. iQ™ relies on the proven syringe tub standard and decreases the need for format parts among others. Therefore, companies could reduce investments and running costs by up to 40% and clean room space by up to 60%. The platform is compatible with numerous machine vendors and includes a versatile portfolio of vials, syringes, and cartridges as well as pre-validated container/elastomer combinations.

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Booth A34
Meeting Data Integrity Requirements

Q: Given the current focus on the subject of data integrity in regulatory inspections, we have performed an internal assessment. We found several pieces of equipment, in particular analytical instruments, which do not meet the requirements (e.g., shared user access). We are concerned whether we can continue using this equipment under these circumstances. Can you advise?

A: Although data integrity is not a new concept, it is true that there has been an increased focus on data integrity in inspections by regulatory agencies globally, and this is very likely to continue unabated. You certainly did the right thing by assessing your current compliance level, which, it turns out, is not in substantial compliance with the regulations.

First, you must determine whether it is acceptable to continue to use these non-compliant systems for the manufacture of pharmaceutical products, and if so, under which circumstances. The regulators encourage a risk-based approach to compliance, though this must not be misinterpreted as being allowed to be non-compliant, rather, this compliance approach requires you to perform a risk assessment (i.e., you need to ascertain the risk to the patients should you continue using your out-of-compliance equipment).

Take for example, a tablet press that has been in operation for 15 years, which is in perfect working order and has no access controls. Anyone working on the machine can change the parameters and edit the stored data. This is not an acceptable situation. Preferably, one would implement technical solutions (perhaps a software upgrade), but where this is not an option or would take too long, one needs to consider procedural remedial actions. In this instance, this could include the verification of the settings by a second person, plus an amendment to the operating procedure, which would clearly define acceptable and unacceptable data handling (e.g., changing parameters). If neither technical nor procedural solutions lead to an acceptable risk level, I’m afraid, this piece of equipment must no longer be used.

Another example would be the use of a laboratory information management system (LIMS) by several operators sharing a user ID and password. If this is the case because of cost savings (purchasing a minimum number of licenses only), then this issue can be remedied almost immediately by purchasing the appropriate number of licenses and revising the operating procedure to mandate individual user IDs and passwords for all LIMS operators.

You did the right first step (i.e., assessing the as-is situation); however, you should not stop there. Now you must implement a company-wide data integrity policy and embed data integrity into your quality management system. Only by taking data integrity seriously, and implementing the appropriate processes, procedures, and systems within your company, will you be able to achieve full compliance with the data integrity requirements. This will give you peace of mind when an agency inspector calls next time. PTE
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