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In Short Supply

Pharma supply chains have been in the limelight lately, as the whole world waits with anticipation for vaccine doses to be delivered and for a resultant light at the end of the pandemic tunnel. News on the supply of vaccines has been varied, with some ‘good’, some ‘bad’, and some ‘ugly’ stories hitting headlines.

The ‘good’
Throughout the pandemic, the bio/pharma industry has proven itself to be adaptable—rapidly progressing vaccines and other therapeutics to help combat and treat COVID-19 and forming partnerships with ‘competitors’ to ensure supply could be maximized. Most recently, three new partnerships have formed: those of Sanofi and Novartis with BioNTech and Pfizer, and Bayer with CureVac (1–3).

In January 2021, Sanofi stated it will perform late-stage manufacturing of the Pfizer-BioNTech vaccine to supply more than 125 million doses for the European Union (1), and Novartis signed an initial agreement to use its aseptic manufacturing facilities in Stein (Switzerland) to produce vaccine doses that will be shipped back to BioNTech for global distribution (2). Bayer revealed its plans to support CureVac with an anticipated additional 160 million doses of its COVID-19 vaccine in 2022, manufactured through Bayer’s network, which includes the company’s site in Wuppertal (Germany) early in February (3).

The ‘bad’
Towards the end of 2020, Pfizer announced a reduction in the expected number of vaccine doses it could deliver due to supply chain issues (4). Then, in mid-January 2021, Pfizer and BioNTech released a statement concerning the upsizing of manufacturing at the Puurs site in Belgium, which would mean modifications of certain production process and a resultant, temporary reduction in the number of doses delivered (5). This news was met with anger by several frustrated European Union member states who urged for pressure to be applied to the companies to deliver the agreed upon number of doses (6).

Further adding to European anxieties that vaccination programmes would be hindered was the fact that AstraZeneca would also not be able to meet the previously agreed upon number of vaccine doses due to production issues in European manufacturing sites, which the company divulged to the EU’s Steering Committee on 22 Jan. 2021 (7).

The ‘ugly’
AstraZeneca’s supply announcement resulted in a public dispute between the pharmaceutical company and the European Commission (EC). While the EC asserted its ‘deep dissatisfaction’ at the revelation from AstraZeneca (8), the company’s CEO, Pascal Soriot, pointed to the contract, which he specified only required the company make “best efforts” to deliver the previously agreed upon number of vaccine doses (9). The confidential contract was published on 29 Jan. 2021 with some information redacted (10).

As the dispute continued, the EU announced that export controls would be placed on vaccines produced in the bloc, including Northern Ireland (NI), heightening tensions between the EU and the United Kingdom and garnering criticism from the World Health Organization (11). Hours after the EU announced these export controls, there was a U-turn on the decision to trigger the safeguard clause, meaning that the Ireland/NI protocol would be unaffected (12). The relationship has somewhat improved between AstraZeneca and the EU, with the company agreeing to supply an additional nine million doses by March (13).

Further industry collaboration, such as the support being offered by Sanofi, Novartis, and Bayer to produce vaccine doses, will be imperative over the coming months to help with supply issues and bolster efforts to tackle the pandemic.

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EUROPEAN REGULATORY WATCH

Getting Tough on Supplies

The EC intends to get tougher on issues such as reliability of drug supplies, particularly essential medicines.

Europe will be hoping to see the suppression of the COVID-19 virus in 2021 with a drastic fall in infections, hospital admissions, and deaths. The virus suppression should then trigger an economic recovery, big enough hopefully to save the region from a deep recession.

The ending of the pandemic will enable the European Union and neighbouring countries to move ahead with a legislative agenda aimed at tackling some of the region’s major public health problems. Once COVID-19 has receded to the background, the virus suppression should then trigger an economic recovery, big enough hopefully to save the region from a deep recession.

The European Commission (EC), which makes proposals for new legislation and guidelines, has indicated that the EU intends to take a much tougher line on issues like reliability of drug supplies, particularly on essential medicines (1). The new policy could have a major impact on future relations between the EU and national governments, and the industry.

The EC is calling it an EU Health Union in which the prevailing ethos will be one of countries working together rather than individually. In fact, the commission will be given much more control over EU public health, which traditionally has been overwhelmingly the responsibility of individual member states.

**COVID-19 vaccines**

Over the thorny issue of supplies of COVID-19 vaccines, which first became available in late 2020, the EC persuaded 27 EU member states in June 2020 to back a €2 billion joint procurement of sufficient doses to meet the needs of the whole of the EU (2). The only country not to participate was the United Kingdom, which finally left the EU at the end of the year. Instead, the UK reached its own deals with a number of vaccine manufacturers (3). One of the deals struck by the UK was with AstraZeneca, which was developing a vaccine jointly with Oxford University to be manufactured in the UK (3). Another deal was reached by the UK for a vaccine jointly developed by Pfizer and BioNTech of Germany (3).

In January 2021, AstraZeneca and Pfizer/BioNTech announced that they were having to make production changes. Though denied by the companies, these changes could result in their not fulfilling supply contracts—advance purchase agreements (APA)—with the EU on time (4). The announcements of reduced supply came even after the EU had put up money to ensure the companies had sufficient manufacturing capacity (5).

The EC reacted furiously to the announcements, particularly to the news from AstraZeneca, which Health Commissioner Stella Kyriakides said could result in “considerably” fewer doses being supplied in the first quarter of this year (6). The expected reduction is widely reported to amount to 75 million doses out of the 300 million doses with an option for another 100 million in the EU-AstraZeneca deal.

“Pharmaceutical companies, vaccine developers, have moral, societal, and contractual responsibilities, which they need to uphold,” said Kyriakides in a statement (6).

After Pascal Soriot, AstraZeneca’s chief executive, claimed in an interview (7) in January 2021 with the Italian newspaper La Repubblica that the EU contract only committed his company to make its “best efforts” to deliver the agreed supplies on time, the EC demanded that in the interests of transparency AstraZeneca publish the text of its APA (8). The need for more transparency is likely to be a constant theme in the EU’s future demand for greater reliability of drugs supplies.

The text of the contract published on 29 Jan. 2021, with confidential details on prices, costs, and output redacted, confirmed that AstraZeneca had agreed to use its “Best Reasonable Efforts” to manufacture the contracted doses at its manufacturing sites in the EU. These sites comprised facilities in Belgium and the

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Controlling exports

On the day the contract was published, the European Medicines Agency (EMA) gave conditional approval to the AstraZeneca vaccine for use by all patients over 18 (9). At the same time, the EC published details of a system for authorizing the export of vaccines subject to APAs because of “a risk that vaccines produced in the Union are exported from the Union, in particular to non-vulnerable countries” (10). Such a potential breach of contractual commitments made by pharmaceutical companies could cause shortages and therefore delays in the administration of vaccines to EU patients, according to the commission.

The planned export curbs, together with the information that companies would need to provide to the authorities, were already arousing concern in the industry before their details were published. “It is vital that any measures proposed by the commission do not restrict or have other negative impacts on exports of vaccines or the import of key vaccine manufacturing supplies,” said the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Vaccines Europe in a joint statement on 27 Jan. 2021 (11). “[This is particularly the case] given the importance of global supply chains in delivering vaccines to citizens in Europe and the world.”

The scheme under which vaccine exports are having to be approved by national authorities in consultation with the EC will be in force only until 31 March 2021 (10). The commission has not ruled out an alternative system of control being introduced after that. “The aim is to provide us immediately with full transparency—transparency that until now has been lacking and which Europeans expect,” commented Valdis Dombrovskis, EU trade commissioner, in a press release (12).

COVID-19 vaccine producers are having to tell national authorities, which in some countries are the government’s health ministries, details of their export plans including amounts, destinations, and dates of delivery. In addition, they are being expected to give information about their vaccine exports over the previous three months (10).

Vaccine exports to certain countries, mainly neighbouring non-EU states, are being exempted from the new rules. Sales to international funds to finance supplies to poorer countries are also being allowed. The major exception among the neighbouring states is the UK, which had a vaccination rate of 12% in late January against 2.5% in the EU (13)—a gap which made the commission the target of much criticism by irate EU citizens.

Foundation for improvement

The EC wants to use the lessons learned from the COVID-19 pandemic as a foundation for a legislative programme aimed at improving healthcare in the EU with dealing with medicine shortages and inadequate access to innovative treatments prioritized.

There are a range of underlying causes of scarcities to be tackled—such as parallel trade, shortages of APIs, supply quotas, levels of prices and reimbursements, and even companies’ marketing strategies. Many of the legislative choices could be directed at stronger obligations on industry to ensure supplies, earlier notification by companies of impending scarcities, and enhanced transparency of stocks along supply chains.

However, the COVID-19 pandemic has made clear that the most urgent health policy requirement in Europe is the creation of a system for dealing with vaccine and medicine supplies during major health crises.

Despite its wealth, Europe has been among the regions that has suffered the most from COVID-19. By early 2021, it had a cumulative total of approximately 20 million cases and 500,000 deaths, with the UK having the highest death total of over 100,000 in January 2021, followed by Italy with 85,000 and France 73,000 (14).

The EC has been looking at ways of extending supply systems during emergencies to cover not just medicines but other essential products, while at the same time ensuring they are highly secure and resilient. It has been considering the feasibility of combining with non-EU members of the World Trade Organization to set up more coherent global supply chains (1).

Without some sort of solution, it will not just be Europe that will be in danger of descending into trade wars over supplies of vaccines.

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Despite the limitations set by the COVID-19 pandemic, bio/pharmaceutical manufacturers achieved unprecedented speed in developing new products in 2020. This was most evident with the first two COVID-19 vaccines, which reached the public under Emergency Use Authorization in December 2020. Where developing a vaccine has traditionally required 10 years, Pfizer-BioNTech and Moderna Therapeutics cut that time to less than a year (1,2) with their messenger RNA (mRNA) vaccines.

Developers attribute this speed to developers’ willingness to assume more risk from the start and to leverage years of past research and clinical experience with the platforms themselves (e.g., mRNA or, in the case of Johnson & Johnson’s (J&J’s) COVID-19 vaccine candidate, with human adenoviral vector [Ad26]). With J&J’s vaccine, cell-line optimization was also crucial, not only for speeding the vaccine’s development but for optimizing its manufacturability and stability, as Paul Stoffels, executive vice president and chief scientific officer told attendees at the 2020 Galien Forum (3). Stability was optimized to levels of 2-8 °C, simplifying global distribution to developing nations.

However, with COVID-19 vaccines and therapies, the greatest increases in agility were achieved on the clinical side. New adaptive clinical study models were used; some early testing in humans was done concurrently with animal testing; some safety tests were run simultaneously with efficacy tests, and elements of Phase II and Phase III trials were combined. On the preclinical side, work on Moderna’s COVID-19 vaccine was accomplished within a few months (3), CEO Stéphane Bancel explained at the 2020 Galien Foundation Forum. Scientists had sketched the experimental design in January 2020, the first test product was sent to the US National Institutes of Health in February, and Phase I testing started in early March. By the autumn of 2020, chemistry, manufacturing, and control (CMC) documentation had been submitted to The United States Food and Drug Administration (FDA) while safety testing was still going on.

Setting the bar higher for R&D
So far, successful projects have wrapped up clinical phases in 12 to 18 months, according to Boston Consulting Group (BCG) analysts (4), setting the bar high for bio/pharma R&D in general. One question is whether achievements made during a time of crisis can be sustained after the pandemic and move into mainstream bio/pharmaceutical development. BCG analysts see success depending on whether companies adopt three basic best practices: taking virtual approaches; leveraging real-world patient and healthcare evidence; and embracing new work...
practices. They believe that companies must adopt four practices in order to make this agility permanent:

- **Take an end-to-end view of drug development**
- **Build and sustain talent**
- **Ensure that their view of drug development is an evolving one**
- **Work more closely with regulators.**

It will likely take two to three years for the bio/pharmaceutical industry to adopt these practices, but the analysts expect them to cut 4–5 years off the average time required for clinical trials.

**Building on pre-COVID trends**

However, these new approaches build upon a foundation that was put in place before the pandemic hit (5), based on increased use of biomarkers and better patient targeting during clinical stage planning. In addition, more bio/pharma companies have been using data analytics, including artificial intelligence/machine learning (AI/ML), which can be applied to real-world data from such diverse data sources as electronic health records, lab test results, and insurance claims, to ensure that trial design and patient recruitment reflect actual conditions.

Efforts by the European Medicines Agency (EMA), FDA, and other regulatory agencies to adopt newer approaches and collaborate more closely with industry to speed review of important new drugs have also helped shrink development timeframes. Over the past few years, EMA and the Heads of Medicines Agencies have analyzed the potential impacts of data analytics on drug development, as well as regulatory review (6). Regulators in the European Union have supported adoption of innovative methods and technology, as has FDA.

In a speech on 1 June 2020 (7), former FDA Commissioner Stephen Hahn pledged to make permanent some innovations that the industry and agency have made to increase agility during the pandemic. He emphasized decentralized clinical trials and use of real-world data in clinical trials. New technology is becoming increasingly important in optimizing clinical trial study design, site selection, and patient recruitment. It is also proving its worth in predicting R&D and clinical outcomes, to help prioritize, early on, the most promising candidates, says Natalia Kotchie, vice president of R&D Applied Data Science Center at the contract research organization (CRO), IQVIA.

**Assuming increased clinical and business risk, but managing it well, brought unprecedented gains in clinical trial and overall drug development speed in 2020.**

Moderna used predictive models in the earliest phases of its COVID-19 vaccine development planning (3). Meanwhile, in its work with bio/pharma clients as a CRO, IQVIA has been developing AI/ML-based tools and systems for the past five years to optimize clinical trials. During the pandemic, IQVIA-developed COVID-19 models have informed trial operational planning choices, depending on areas where COVID-19 outbreaks were most likely to occur, says Kotchie.

**Closer collaboration**

For bio/pharma companies, one fundamental change that is speeding drug development has been increased collaboration and cross-learning through partnerships, says Lance Minor, national co-leader of life sciences practice for the management consultant, BDO USA LLP. The industry has engaged in collaborative research for decades, but during the current pandemic, the level of collaboration has intensified.

One new alliance is CARE, for Corona Accelerated R&D in Europe, which was established to accelerate development of treatments for COVID-19. The five-year project involves 37 global partners and is led by the French National Institute of Health and Medical Research, Janssen Pharmaceutical NV, and Takeda Pharmaceuticals. Other collaborative projects have brought together such competitors such as Roche and Regeneron, Gilead and Roche, Gilead and Pfizer, Sanofi and GlaxoSmithKline (GSK). Bio/pharmaceutical companies are also working together in incubators established by the World Health Organization, the Global Alliance for Vaccines and Immunizations, the Coalition for Epidemic Preparedness Innovation, and the Gates Foundation (8). Meanwhile, closer ties with CROs and healthcare organizations have added another dimension to collaboration, Kotchie says.

**Increased tolerance of risk**

Another factor speeding development of COVID-19 treatments and vaccines has been developers’ increased tolerance for risk, not only on the financial side, but in the clinic, Minor says. Pfizer-BionTech and Moderna spent billions of dollars on development for COVID-19 vaccines, but they also took risks by changing the traditional sequential approach to clinical testing, he explains.

In 2020, assuming these risks, but managing them, paid off in shortened development times. In 2021, novel approaches to enrolling patients and use of remote patient monitoring should also have an impact, he says. Although programmes in 2020 focused on therapies and vaccines for COVID-19, the pace of other clinical projects will pick up in 2021, Minor predicts.

Success in a challenging year has led to optimism for 2021. In BDO’s 2021 survey (9) of 100 chief financial officers (CFOs) at medium-to-large life sciences companies, the company found that 69% plan to increase spending on R&D, most of them singling out three or four promising commercialization targets.

Pharma companies are still planning to increase investment in the development of new COVID-19 treatments (mentioned by 43% of respondents to the survey) and vaccines (a key investment focus for 45% of the CFOs surveyed), but a larger number also plan to invest in other therapeutic areas, with 57% mentioning
cell therapies (up from 41% in 2020) and 56% targeting immunotherapies (up from 32% in 2020) (9). The importance of digitization was reflected in survey results, with 63% respondents saying that digital transformation would be their leading growth strategy in 2021.

One innovation that has helped shorten drug development timeframes has been use of biomarkers (10), which EMA and FDA have supported since the early 2000s. On 30 Nov. 2020, FDA established a new pilot programme, the Innovative Science and Technology Approaches for New Drugs (ISTAND) (11), designed to help break through some of the industry’s reluctance to use technologies that have not first been applied in approved new drug applications.

Through ISTAND, technology developers can apply to FDA for qualification of a novel technology for a specific use. The new pilot would cover new, nontraditional methods of data collection or analysis methods; technologies such as tissue chips that serve as micromodels of specific organ systems for safety tests; and use of artificial intelligence and wearable sensors, which could be used during clinical trials.

To strengthen its foundation for data analytics, FDA has been working with vendors on initiatives in the food import screening and medical devices areas. For pharma, key targets are drug safety testing during clinical development. In December 2020 and January 2021, the agency entered into contracts with Palantir and SAS to focus on building the data foundation required (12,13). Big Pharma companies, including Novartis, Roche, Merck, Pfizer, AstraZeneca, and GSK have also been actively working in this area (14).

Among the challenges for pharma companies that have already embraced new technology is finding, cleaning, and reorganizing data to be research-ready so that AIML platforms can yield useful results, says Kotchie. Also required, she says, will be the ability to translate business problems to how users make decisions. The goal is to ensure that their experience of new systems enhances users’ ability to maximize the application of the models developed. “This is an area that the new [data science] discipline of ‘decision intelligence’ is helping us to address,” she says.

**Managing clinical risks**

All the enhanced clinical trial flexibility seen during the COVID-19 pandemic has had to be balanced by strict risk evaluation and management. CROs have worked more closely with customers to manage the many risks posed by the COVID-19 pandemic and to ensure the success of clinical trials. Business continuity programmes have been crucial, says Teresa Lamentia, senior vice-president of operational transformation and performance at IQVIA, who also leads the company’s COVID-19 task force for R&D.

IQVIA’s clients range from small innovators to large pharma companies, and although some firms had to halt clinical projects in 2020, most have restarted efforts, she says. “We’re not back to previous levels, but clinical trial recruitment is definitely increasing and this trend should continue in 2021,” she says. Lamentia and her team have taken a three-pronged approach to examining every trial protocol, from the standpoints of patient safety, data integrity and robustness, and day-to-day realities affecting sites (e.g., procedures to ensure that subjects receive trial drugs and have necessary tests performed when COVID restrictions cause a site to be shut down). Detailed reports were then developed to ensure that risks did not impact pharma clients or patients. As she notes, the company had to adopt remote approaches for dosing and patient testing, and wound up taking a hybrid approach combining on-site and remote elements. This method demanded that both the CRO and pharma company pay close attention to supply chain issues, she says.

For IQVIA, an especially challenging problem was the sourcing of personal protective equipment and ancillary products for technical and business staff. Conformance with patient data protection regulations has been another challenge, although a growing number of tools are available and in use that allow the safe use of patient data, says Kotchie.

In general, clinical trials are being run to optimize flexibility. “Taking an ‘umbrella’ approach to protocols lets us perform more tests concurrently,” Lamentia notes. However, it is not yet clear which new methods adopted during the pandemic’s first year will become permanent best practices, she says. Lamentia expects to see more remote study approaches and more flexible clinical trial designs dominating drug development in the future. Based on regulatory and corporate plans, data monitoring and analytics promise to play an increasingly important role as well.

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Rapid growth in biopharmaceuticals, an increasingly complex drug landscape, and rising expectations for administration convenience by the consumers, are all contributing factors that are driving demand for new delivery solutions across the bio/pharma industry. “The market continues to shift towards the development of complex oral and complex parenteral drug products that require advanced drug delivery technologies and functional excipients to improve targeting, enhance performance, or eliminate the need for boosters in vaccine applications,” explains Maaike Everts, strategic marketing leader for parenteral drug delivery at Evonik.

Drivers of development

“The past couple of decades have seen a rapid growth in both biologics and biosimilars as treatments for a variety of conditions,” asserts George I’ons, head of product strategy and insights, Pharmaceutical Services, Owen Mumford. As a result of the composition of biologics, drug delivery is typically limited to intravenous injections, which is considered to be less convenient for the patient. Therefore, work is being done on the development of more convenient routes of administration, such as subcutaneous (SC) injections rather than intravenous (IV).

Behzad Mahdavi, vice-president open innovation biologics, cell & gene therapy, Catalent, agrees that changing the route of delivery, to either SC injections or oral delivery, is a key driver in the field of biologics. “The technologies and approaches therefore vary in this category from having to formulate the drug at a high concentration in a smaller volume by simple viscosity reduction, to the use of more complex systems that integrate several mechanisms of actions to counter different barriers in the gastrointestinal tract,” he says.

“The second driver [for biologics] is targeted delivery, to assure that the drug reaches its target and delivers its therapeutic efficiently,” Mahdavi continues. “In contrast to small molecules, where formulators are able to optimize therapies to suit a certain patient group, biologics are personalized right from the start during therapy design.”

In concurrence, Arul Balasundaram, formulation manager at Recipharm’s Queensborough facility (United Kingdom) emphasizes the need for development of delivery solutions that can achieve more effective, targeted, and controlled release within target parts of the anatomy. “Large-molecule drug substances are becoming more complex, presenting both manufacturing and formulation challenges—particularly both the inherent difficulties in ensuring the drug’s stability until it reaches the target organ and administration convenience,” he says.

When considering small-molecule therapies that are already available and approved, there are numerous drivers for the development of novel delivery solutions, such as variation in the therapeutic need of the formulation for new target patient groups (i.e., geriatrics or paediatrics), notes Andrew Parker, director Open Innovation, Small Molecules, Oral and Specialty Drug Delivery, Catalent. “In addition to dosing requirements, other drivers include the need for a different delivery profile (for example extended release) to enable a better area-under-curve for therapeutic effect; adjacent therapy target requiring modification of the delivery platform (e.g., different in-vivo target such as the lymphatic system); alternative delivery platforms to enable a faster onset (e.g., inhaled versus oral administration); second-generation formulation to improve on any relative weaknesses in the initially marketed products; and intellectual property drivers such as evergreening a delivery portfolio based on a specific API,” he says.

Delivery advancements

The well-documented rise in poorly water-soluble drugs entering the development pipeline over the past few decades has led to advancements in ways that APIs in an improved ‘bioavailability-enhanced state’ are
delivered, Parker notes. “These [advances] include building on well-known delivery technologies such as spray drying, hot-melt extrusion, and the use of lipidic systems, with excipient manufacturers developing improved polymers that are tailored to improve processing and/or solubility, enhance stability, or improve performance in vivo for APIs with solubility challenges,” he says. “Additionally, new ways to process materials such as supercritical fluid processing are also possible under CGMP [current good manufacturing practice] conditions in the pharmaceutical industry that can impart desired attributes based on particle size, shape and morphology, to further aid with delivery of poorly water-soluble molecules.”

For Lynn Allen, vice-president Business Development, MedPharm, de-risking the development process has been important in helping to speed up timescales and enabling faster patient access to critical treatments. Although in-vitro performance testing models have been used for some time in the industry to screen new actives and optimize formulations, MedPharm has been applying the models to de-risking clinical trials for products targeting skin, eye, and mucosal membrane diseases, Allen states. “These models allow developers to screen with significant throughput for the activity and potential side effects of drug products against key pathways as well as understand their pharmacokinetics early in the development programme,” she says. “Crucially, they provide this information using viable human tissue thereby greatly reducing the need for expensive animal and human safety/efficacy studies.”

Many new technologies are being explored for drug delivery and approaches are being assessed for new skin, buccal, and nasal membrane delivery methods, adds Ralph Landau, head of development, Drug Product, Cambrex. “Controlled drug delivery has long been pursued in the industry, but this still has challenges to overcome from dose-dumping, erratic dissolution, and food effects. Today, modified-release coating ingredients can now be modulated to enable greater precision for dosing the drug substance in targeted areas of the gastrointestinal tract,” he says.

“Further development of modified-release dosage forms will enable the delivery of these molecules to a specific site of treatment. This [targeted delivery] will ensure that the therapy is introduced and actively initiated at the right time and place to disrupt the disease with precision and minimal impact to the patient.”

“The new delivery advances to target drug delivery to specific organs and tissues has helped the formulators in improving therapeutic response and bioavailability with site-specificity,” Satish Shetty, director of Product Development, Cambrex adds. “The availability of biodegradable polymers enables development of new dosage forms that overcomes physiological hurdles.”

Ophthalmic drug delivery is a specific area where advancements are providing significant opportunities, according to Everts. “Recent advances in formulation, process, and manufacturing technologies are enabling significant opportunities to better maintain effective therapeutic concentrations over time and reduce the total number of injections,” she states. “Enhancements in polymers and other biomaterials are also encouraging the formulation of hydrophobic and hydrophilic drugs that can precisely match the desired release profile, allowing the incorporation of drugs with high potency by reducing systemic side effects.”

Additionally, Everts underlines the use of lipid nanoparticle (LNP) technologies as a particular highlight of 2020. “For parenteral drugs, one of the highlights of 2020 was the use of LNP technologies to enable the rapid development and emergency use authorization of the first mRNA vaccines for COVID-19,” she says.

The momentum that has been seen in the area of LNPs is expected to continue in the future for the delivery of nucleic acids, gene and cell therapies, and other nanomedicines, Everts notes. “However, to maximize this opportunity for LNPs, challenges relating to stability, shipping, storage, and one-time administration need to be addressed,” she continues.

“So, we expect to see many industry innovations focused on formulations that can be stored either at normal refrigeration or room temperature, and then remain stable for several months or more.”

The recent use of mRNA technology in the treatment of COVID-19 has paved the way for formulators to target other infectious diseases, according to Balasundaram.

“Advancement in nanotechnologies has enabled the formulators to use drug carriers, such as nanoparticles, liposomes, dendrimers, nanowafer, and hydrogels to deliver proteins via non-invasive drug delivery routes,” he says.

“Biologics are increasingly being developed with the aim of reducing the frequency of administration in order to improve patient acceptance and also in turn increase adherence,” stresses I’ons. “To achieve this, the formulations often require either higher volumes (typically over 1 mL) and/or higher concentrations, and hence increased viscosities.”

To overcome the issues associated with increased viscosities, drug delivery devices have been developed that can accommodate a primary container with larger fill volumes and effectively deliver high viscosity formulations, I’ons states. “Newer designs in autoinjectors and prefilled safety devices that satisfy these requirements, and allow delivery of these more complex formulations, are emerging on the market,” he says.

Also, alternative devices to conventional spring-based autoinjectors have been developed to facilitate the delivery of highly viscous parenteral formulations, confirms Balasundaram. “There is also a lot of work going on to help formulators who need to deliver high dose formulations.
as one dose, for example the development of electronically enabled delivery devices such as patch-pumps to deliver several mL over minutes,” he adds.

Mahdavi adds that there are some macromolecules that can now be delivered orally, overcoming the permeability and stability challenges in a more easily administered form than injections. “The use of surfactant-based permeation enhancers may improve the permeability of large-molecule APIs, and when combined with enteric coating, prevent degradation of the encapsulated formulation in the stomach,” he says. “In turn, this benefits the patient through reduced dosing complexity, improved safety, and better adherence.”

**Targeted approaches**

Having the ability to target a drug to a specific site within the body or for it to be released at a certain time provides many advantages. “Targeted delivery of drugs not only means less API is needed to be delivered to generate a desired therapeutic effect, but also a lower risk of off-target toxicity issues being observed in a patient,” Parker reveals. “Additionally, targeted delivery may facilitate lower dosing regimens and a corresponding reduction in a patient’s burden of compliance.”

“Multiple approaches are available for the targeted delivery of drugs, with varying degrees of precision, from highly-targeted approaches such as antibody-drug conjugates (ADCs), to LNPs that offer degrees of affinity,” emphasizes Mahdavi. “There are also novel targeting approaches being researched or undergoing early preclinical testing, including natural nanoparticles such as extracellular vesicles. It is important to note that in order to get high efficacy, other aspects such as stability and efficient release of the drug payload before and after reaching the target are key considerations.”

Some of the techniques and solutions that are currently available to formulators for targeted drug delivery include microencapsulation, microsponges, nanotechnology, immunoconjugates, and viruses, reports Shetty. These targeted delivery approaches are important in pharmaceutical research to overcome solubility issues, protect the drug from the environment and pH changes, prevent dose dumping by controlling the release profile, control targeting at the site of action, and improve patient compliance, he says.

Employing a disease or route of delivery specific performance model can help formulators target specific objectives, states Allen. “If we focus on nasal delivery, historically the industry has been reliant on models of nasal drug performance that are limited in their ability to present a more complete picture of nasal drug delivery. Although the passive barrier remains intact within these models (e.g., simple cell monolayers), active components such as cilia, tight junctions, mucus production, and other cellular activities do not,” she notes. “Reconstituted nasal epithelial (RNE) models present an improved version of this model system. To more closely mimic the in-vivo physiology, cell signalling, and architecture, primary human nasal epithelial cells are regrown on permeable inserts and stimulated to develop into a well-differentiated nasal epithelium cell.”

Through the continuous development of models, such as RNE, formulators are being afforded the opportunities to expand the techniques and possibilities available for targeted drug delivery, Allen stresses.

Balasundaram believes that there will be a greater number of products designed for a local effect in the near future. “Different dosage forms for local effect are very useful when it comes to achieving a high drug concentration in the target organ,” he says. “For instance, inhalation products are very useful not only when treating respiratory diseases, but also central nervous system diseases.”

A targeted delivery approach that has proven to be successful in the eye of Everts is local drug delivery, whereby sustained-release formulations are applied onto specific anatomical areas, such as the knee, eye, and sinus. “With this approach, efficacious drug concentrations are maintained at the site of administration for weeks and months,” she says.

“Another successful approach is passive targeting,” Everts adds, “for example, targeting the liver by achieving liver uptake of drug-loaded nanoparticles following intravenous administration.”

In addition, active targeting is a useful approach to deliver a drug to specific cells or cellular compartments such as tumour cells, immune cells that can be stimulated for immunotherapy, or to deliver gene therapy drugs to the nucleus versus the cytoplasm of a cell, Everts states. “Achieving active targeting is a challenge and requires the development of complex parenteral formulations that will continue to rely upon existing and novel functional excipients, understanding, and overcoming biological barriers, optimizing new emerging drugs, such as nucleic acids, and developing manufacturing processes that can be scaled up for commercial success,” she says.

**Progressive solutions for biologics**

The biologics market is becoming more saturated, and it is expected that there will be many more large molecules in development in the near future. As a result of this market saturation, developers will be seeking more ways to deliver these complex drugs. “When considering oral delivery as a possible administration method for future biopharma treatments to avoid parenteral delivery, avoiding degradation in the harsh gastrointestinal environment, as well as transporting large and hydrophilic biologic molecules into the bloodstream remain major barriers to development,” stresses Balasundaram.
Research has been undertaken by MedPharm experts (1), demonstrating the ability for some aptamers to penetrate the skin irrespective of their large molecular weight, Allen reveals. “This research offers hope for the discovery of new treatments of difficult-to-treat dermatological diseases,” she says. “There is a tremendous amount of effort to prove these diseases can be treated with targeted topical delivery.”

Additionally, research into nasal or inhaled delivery of biologics is ongoing and has the potential to lead to a new generation of inhalation biopharma therapies, confirms Balasundaram. “Possible examples include the delivery of gene therapy to the lungs, as well as inhaled insulin,” he says.

However, the oral route of administration remains the most preferred, due to convenience, cost-effectiveness, fewest sterility constraints, relative flexibility in the design of the dosage form, and ease of production, states Mahdavi. Innovative approaches that can overcome the three main obstacles to administering biologics orally—digestive enzymes in the gut that can destabilize the molecules, the physical barrier of the thin mucus in the gut, and the tight junctions of the gut cell wall lining that prevent transportation of proteins—would be game-changing in drug delivery of large-molecule products. “A combinational integrated technology containing enteric coating, protease inhibition and absorption enhancement will continue to have an enormous impact on oral delivery of biologics,” he notes.

Thanks to recent improvements in the understanding of the human genome, in addition to advanced diagnostic and analytical tools, the biologics market is positioned for explosive growth over the coming decade, Everts declares. Even though the majority of biologics entering the market are using parenteral routes of administration, limiting therapeutic applications to areas where no oral standard of care is available, efforts are underway to facilitate the oral delivery of peptides, antibodies, and nucleic acids, with most platforms in early, pre-clinical stages, she confirms.

“However, there are some encouraging developments using either polymeric or lipid-based excipients that will protect the biologic from acid and enzymatic degradation, increase contact time with epithelium to enhance absorption and increase mucosal permeability,” Everts says. “The coming years will provide greater clarity as to which platform technologies will provide the right balance between safety and efficacy.”

Reference
The US Pharmacopeia and other major pharmacopoeias have established that only the combination of documentary standards and pharmacopeial reference standards (RS) is conclusive and determines compliance to their official quality requirements. Therefore, the use of non-pharmacopeial RS with pharmacopeial methods is inconclusive, and the user takes responsibility at their own risk. Secondary RS are often used for qualitative and quantitative purposes. This article provides an overview of the key risks that can be associated with the use of secondary RS based on the measurement uncertainties that are intrinsically connected to the approach, and information that might help mitigate these risks to some extent. Case study examples are included to illustrate scientific challenges associated when transitioning from pharmacopeial RS to secondary RS. The guard band principle is discussed as an evocative way to visualize risk.

The Value of Pharmacopeial Reference Standards

Christian Zeine, Doug Podolsky, Jane Weitzel, Ravi Reddy, and Steven L. Walfish

To ensure the safety and efficacy of APIs and their finished dosage forms, these pharmaceutical articles need to be of a certain quality. The United States Pharmacopeia (USP) and other pharmacopoeias establish public compendial standards to ensure quality requirements. Such compendial standards and their revisions are established in a transparent process. These standards are of high relevance, as they help facilitate access to affordable medicines (1), and they almost always have official status. At the same time, they are of high value to the pharmaceutical industry because they also decrease the development effort of pharmaceutical articles (2). The value of compendial standards is also described in a recent white paper authored by the World Health Organization International Meeting of World Pharmacopoeias (3).

Typically, a compendial standard is a combination of a documentary standard, such as a monograph or general chapter, and an associated physical reference standard (RS). These pharmacopeial RS are primary RS and are established by a rugged collaborative testing approach; they have official status when connected to compendial documentary standards (4) and are, therefore, generally accepted by regulatory authorities without additional qualification by users. When assessing the compliance of a pharmaceutical article against the official compendial standard, only the combination of documentary standard and pharmacopeial RS is conclusive. For example, the European Pharmacopoeia (Ph. Eur.) general text 5.12 states that (5):

“A Ph. Eur. reference standard referred to in a monograph or general chapter represents the official standard that is alone authoritative in case of doubt or dispute.”

The United States Pharmacopeia (USP) General Notices under 5.80 points out that (6):

“Where USP or NF [National Formulary] tests or assays call for the use of a USP Reference Standard, only those results obtained using the specified USP Reference Standard are conclusive.”

Consequently, the use of other (i.e., unofficial) RS in combination with a documentary standard is not conclusive or authoritative. The release or compliance assessment of a pharmaceutical article based on such a combination is the responsibility of the users and is their risk alone, which would also
apply when secondary RS are used, even if they were derived by comparison with the corresponding pharmacopeial RS.

The purpose of this article is to provide case study examples to illustrate scientific challenges associated with transitioning from pharmacopeial RS to secondary RS. This topic is approached from the perspective of measurement uncertainties that are connected to reportable values obtained using compendial standards and how this might change when transitioning from pharmacopeial RS to secondary RS. Calculations for measurement uncertainties for the use of compendial standards are provided in the Methods section, and information on the challenges of transitioning from pharmacopeial to secondary RS are provided in the Discussion section. Only uncertainties for characterization of the pharmacopeial and secondary RS and assay result of substance tested will be discussed in this article. There are other contributions to uncertainties that may influence a measurement, such as contributions for the RS from homogeneity and long-term stability (7), but these are not considered in this paper.

The authors are aware that the calculations performed here are beyond most users for technical reasons. Uncertainties for pharmacopeial RS are not provided, as it is unnecessary for their official use in the monograph. Pharmacopeial RS are not tailored to assign assay values to secondary RS or to set up a traceability relation between them, as these are non-compendial applications. Therefore, it is difficult for users to assess the impact that the switch from pharmacopeial RS to secondary RS would have on the acceptance criteria. This limitation has been clearly pointed out to the pharmaceutical community (8). Nonetheless, the impact on acceptance and rejection zones can be visualized by this approach in an evocative way.

METHODS
The authors examined several USP RS and their relevant data for the calculation of the assigned value. The following exemplary cases illustrate the differences between two types of models used for the calculation of the assay value of the primary RS:

- Type 1 follows a model where all impurities were determined on a percent weight-per-weight (w/w) basis and simply subtracted from 100%(w/w).
- Type 2 follows a model where the chromatographic impurities were considered as relative percentages. Every other contribution (e.g., water, residue on ignition [ROI]) was considered as w/w percentages, to be subtracted from 100%(w/w) before multiplying with the chromatographic purity.

A real compendial RS was selected to represent each type. For confidentiality reasons, they are referred to in this paper as Surrogate Hydrochloride (HCl) RS for type 1 and Replaces RS for type 2.

The assay value of the substance tested (ST) is calculated as shown in Equation 1 and has two components:

$$ST = R \times P$$  \hspace{1cm} [Eq.1]

The first is a ratio (R) often of areas, response factors, or a relative potency comparing the substance tested to the primary reference material. The second comprises the multiplication of the ratio by the value assigned to the primary (P) RS, in this case the pharmacopeial RS, which establishes the reportable value for the substance tested. Both components contribute to the uncertainty of the value assigned to the substance tested, but only the magnitude of the former is within the control of the company developing or adopting the analytical method (9).

As described in Section 8.2.2 of the Eurachem Guide on Quantifying Uncertainty in Analytical Measurement (QUAM) (10), the general relationship between the combined standard uncertainty $u(y)$ of a value $y$ and the uncertainty of the independent parameters $x_1, x_2, ..., x_n$ on which it depends is shown in Equation 2:

$$u_c(y(x_1, x_2, ..., )) = \sqrt{\sum_{i=1,n} c_i^2 u(x_i)^2}$$  \hspace{1cm} [Eq.2]

Here, $y(x_1, x_2, ..., )$ is a function of several parameters $x_1, x_2, ...,$, and $c_i$ is a sensitivity coefficient evaluated as $c_i = \frac{\partial y}{\partial x_i}$, the partial differential of $y$ with respect to $x$. Applied to Equation 1, the combined standard uncertainty of the measurement result for the substance tested can be calculated using Equation 3 (9):

$$u_c(St(R, P)) = \sqrt{P^2 u_R^2 + R^2 u_P^2}$$  \hspace{1cm} [Eq.3]

For Equation 3, the uncertainties for the ratio, $u_R$, and for the assay value of the primary RS, $u_P$, need to be determined. The assay value $P$ can be taken from the information provided from the supplier of the RS or from calculations from other sources. For the purpose of this article, the value for the ratio R can be set to 1, as typically peak areas of similar size are compared.

For the pharmacopeial RS shown in the following sections, all measurements relevant for the calculation of the final assay value were determined in three different laboratories (i.e., standard deviations were obtained on the precision level of reproducibility). Uncertainty was calculated using the (relative) standard deviations of these measurements.

Uncertainty calculation for assay value of pharmacopeial RS, case type 1. Table 1 shows the exemplary data for Surroginate HCl RS, including test results of the collaborating laboratories for the tests relevant for the calculation of the assay value. All organic and inorganic impurities (residue on ignition [ROI]), residual solvents [ReS], water by Karl Fischer [KF], organic impurities [I]) were determined as w/w percentages.
Table I. Surrogatine Hydrochloride reference standard and test results of the collaborating laboratories.

<table>
<thead>
<tr>
<th>Surrogatine Hydrochloride reference standard</th>
<th>Lab 1</th>
<th>Lab 2</th>
<th>Lab 3</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residue on ignition, % (w/w)</td>
<td>0.01</td>
<td>0.03</td>
<td>0.01</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Residual solvents, % (w/w)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Water content (Karl Fischer), % (w/w)</td>
<td>4.00</td>
<td>3.43</td>
<td>3.82</td>
<td>3.75</td>
<td>0.29</td>
</tr>
<tr>
<td>Organic impurities, % (w/w)</td>
<td>0.037</td>
<td>0.04</td>
<td>0.045</td>
<td>0.04</td>
<td>0.00404</td>
</tr>
<tr>
<td>Assigned value, % (w/w)</td>
<td>95.95</td>
<td>96.50</td>
<td>96.13</td>
<td>96.19</td>
<td></td>
</tr>
</tbody>
</table>

Therefore, this RS’s assigned value (P) was calculated using Equation 4, subtracting all single impurity contributions from 100% (w/w).

\[
P = 100 \% (w/w) - (ROI + ReS + KF + I) \%(w/w) \\
= 100 \% (w/w) - (0.02 + 0 + 3.75 + 0.04) \%(w/w) \\
= 96.19 \% (w/w)
\]

[Eq.4]

The determination of the combined standard uncertainty for the USP RS follows Rule 1 as explained in Section 8.2.6 of *Europachem QUAM* (10). This rule is used for calculations involving only sums or differences. Equation 5 shows Rule 1, applied to the specific case, using the standard deviations as uncertainty contributions.

\[
u_P = \sqrt{u_{ROI}^2 + u_{ReS}^2 + u_{KF}^2 + u_I^2} \\
= \sqrt{0.01^2 + 0^2 + 0.29^2 + 0.00404^2} \%(w/w) \\
\approx 0.29 \% (w/w)
\]

[Eq.5]

Equation 6 contains both sum/difference and product/quotient parts. As recommended in Section 8.2.7 of *Europachem QUAM* (10), the determination of the combined standard uncertainty follows a combination of the Rules 1 and 2. Therefore, the interim uncertainty for the first part of the product, “(100-(KF+ROI+ReS+GC+C+CE)) % (w/w))”, will be derived separately using Rule 1. For the second part, “(100-I)-100”, only the uncertainty for the organic impurities (I) needs to be considered. These interim uncertainties will then be linked together to the combined standard uncertainty for the USP RS assay value. Equation 7 shows the calculation for interim uncertainty \(u_{int}\) by Rule 1, for the specific part “(100-(KF+ROI+ReS+GC+C+CE)) % (w/w))”:

\[
u_{int} = \sqrt{u_{ROI}^2 + u_{ReS}^2 + u_{GC}^2 + u_{CE}^2} \\
= \sqrt{(0.04^2 + 0.02^2 + 0.01^2 + 0 + 0.06^2)} \%(w/w) \\
= 0.074 \% (w/w)
\]

[Eq.7]

Equation 8 then combines both \(u_{int}\) and uncertainty for the organic impurities \(u_I\) following Rule 2 from Section 8.2.6 of *Europachem QUAM* (10):

\[
u_P = P \sqrt{\frac{u_{int}^2}{P} + \frac{u_I^2}{P}} \\
= 99.65 \% (w/w) \sqrt{\frac{0.074^2}{99.74} + \frac{0.11^2}{99.91}} \\
\approx 0.13 \% (w/w)
\]

[Eq.8]

Table II. USP Replacepam reference standard and test results of the collaborating laboratories.

<table>
<thead>
<tr>
<th>USP Replacepam reference standard</th>
<th>Lab 1</th>
<th>Lab 2</th>
<th>Lab 3</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water determination (Karl Fischer), % (w/w)</td>
<td>0.11</td>
<td>0.12</td>
<td>0.19</td>
<td>0.14</td>
<td>0.04</td>
</tr>
<tr>
<td>Residue on ignition, % (w/w)</td>
<td>0.04</td>
<td>0.05</td>
<td>0.02</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Residual solvents, % (w/w)</td>
<td>0.05</td>
<td>0.06</td>
<td>0.05</td>
<td>0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Replacepam Related Compound H, % (w/w)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Replacepam R-Isomer and other, % (w/w)</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Organic impurities (high performance liquid chromatography), % total detected area</td>
<td>0.21</td>
<td>0.02</td>
<td>0.03</td>
<td>0.09</td>
<td>0.11</td>
</tr>
<tr>
<td>Assigned value, % (w/w)</td>
<td>99.59</td>
<td>99.75</td>
<td>99.61</td>
<td>99.65</td>
<td></td>
</tr>
</tbody>
</table>
To calculate test results and their expanded uncertainties, the assigned values and their uncertainties from Equations 4, 5, 6, and 8 will be used.

**Calculation of test results and expanded uncertainties.** The calculation of test results and uncertainties follows Equations 1 and 3, respectively. In Equation 3, the uncertainty of the ratio $u_R$ is the last factor to be considered.

Ratio R is determined from peak areas, response factors, or a relative potency comparing the unknown sample (ST) to the primary RS (P) (9). For the cases presented here, the ratio is determined by the comparison of the peak areas of both ST and P and, for simplicity, can be set in first approximation to 1 (Equation 9), as typically peak areas of similar size are compared.

$$ R = 1 = \frac{\text{area(ST)}}{\text{area(P)}} \quad \text{[Eq.9]} $$

The uncertainty $u_R$ of the ratio can then be calculated following the previously described Rule 2 (Equation 10). The terms under the root square are the relative standard deviations (RSD) of the chromatographic method used to determine the areas of the main peaks, see also Section 8.2.6 of *Eurachem QUAM* (10). The authors assume a value of 0.2% for the RSD of the method, for both the Surrogatine HCl and the Replacepam, described previously. The actual method’s RSD should be used, but RSDs are typically approximately that size, depending on the precision regime (i.e., repeatability, intermediate precision, reproducibility) used to determine the RSD (see Table III).

$$ u_R = \sqrt{\frac{u_{\text{area(ST)}}^2}{\text{area(ST)}}} + \frac{u_{\text{area(P)}}^2}{\text{area(P)}} = \sqrt{\frac{0.2^2}{100} + \frac{0.2^2}{100}} \approx 0.0028 \quad \text{[Eq.10]} $$

All data are now available to calculate the uncertainty for an assay result using Equation 3 to determine the combined standard uncertainty of a Surrogatine HCl (Equation 11) and of a Replacepam substance (Equation 12).

$$ u_c(ST(R,P)) = \sqrt{P^2u_R^2 + R^2u_P^2} = \sqrt{96.19^2 \times 0.0028^2 + 1^2 \times 0.29^2} \approx 0.40 \% (w/w) \quad \text{[Eq.11]} $$

$$ u_c(ST(R,P)) = \sqrt{P^2u_R^2 + R^2u_P^2} = \sqrt{99.65^2 \times 0.0028^2 + 1^2 \times 0.13^2} \approx 0.31 \% (w/w) \quad \text{[Eq.12]} $$

These combined standard uncertainties are normally reported as expanded uncertainties by multiplying them with a coverage factor (k) of 2 to reflect a confidence level (CL) of 95%, as described in Section 8.3.3 of *Eurachem QUAM* (10). The assay values for substances tested with a pharmacopoeial RS, as discussed previously, would be reported as follows:

- For Surrogatine HCl with an expanded uncertainty of ±0.80% (w/w) (k=2, 95% CL)
- For Replacepam with an expanded uncertainty of ±0.62% (w/w) (k=2, 95% CL)

These expanded uncertainties are of utmost relevance in the following discussion, which introduces the concept of guard bands.

**DISCUSSION**

The principle of guard bands is commonly used in compliance testing. It considers the expanded uncertainties of analytical methods including the RS used, as outlined and calculated in the Methods section. The principle also considers possible risks of false acceptance or rejection, and the desired level of probability for the correct/false acceptance or rejection. From these considerations, decision rules are derived. Guard bands were also suggested for use in pharmaceutical quality control (release testing) (11, 12).

Basically, decisions for correct acceptance/rejection are made on reportable values that have a certain distance from the original specification limits. Figure 1 shows the general concept of guard bands; more detailed information is available elsewhere (13). Ideally, they should be chosen to be as wide as the expanded uncertainty of the measurement to make sure the risk of a false acceptance/rejection stays considerably low. Furthermore, depending on the criticality of the true value being within the specifications, the guard bands can be either positioned inside the specification zone (stringent acceptance zone, see Figure 1) or outside of the original specification zone (relaxed acceptance zone (14). Results within the acceptance zone would lead to the release of the pharmaceutical article; results outside of the acceptance zone would lead to an initial rejection. In case of initial rejection, two events could be distinguished by using the following decision rules, depending on the laboratory’s risk management:

- Results within the guard bands could be considered outside of expectation (OEE) and would trigger a
predefined OOE retesting routine. This is also known as transition decision rule (14).

- Results outside the limits could be considered out of specification (OOS) and would trigger a stringent investigation, according to the predefined OOS routine.

**Guard bands for Surrogatine HCl.** For the example of Surrogatine HCl, expanded uncertainties for the assigned value of the substance tested were described as calculated in the Methods section; however, for monograph purposes they are usually not known to the user and therefore not considered. This situation is illustrated in the Surrogatine HCl monograph example (Figure 2) by showing the uncertainties as guard bands in dotted lines within the monograph’s specification zone. The acceptance zone in this case (i.e., when combining the monograph as documentary standard [DS] and pharmacopeial RS) would be identical with the specification zone of the monograph. Any result outside the acceptance zone would be OOS. However, in practice (and not considered here), laboratories would probably allow a slightly stricter acceptance zone, in particular regarding the lower limit, because they need to make sure that the pharmaceutical article fulfils the monograph specification over its whole lifecycle.

**Figure 1.** Schematic acceptance and rejection zones for simultaneous upper and lower limits. The guard band (g) is usually as wide as the expanded uncertainty for the measurement result.

**Figure 2.** Schematic acceptance and rejection zones for Surrogatine Hydrochloride, a combination of its documentary standard (DS) and pharmacopeial reference standard (RS). Acceptance, specification, rejection, and guard band (g) zones are not to scale; only uncertainties for characterization of the primary RS and assay result of substance tested have been considered.

**Guard bands for Surrogatine HCl with a secondary RS.** The scenario would change if a secondary RS is used, compared to the pharmacopeial RS for its assigned value (Figure 3). Adding that additional measurement step results in a larger uncertainty for the secondary RS. Consequently, the expanded uncertainty for the overall measurement increases as well. The outcome is an extension of the guard band (i.e., a narrowing of the acceptance zone). Again, this narrowing is usually not known to the user. However, as per definition, only results obtained with the original pharmacopeial RS are conclusive; there is a real risk of obtaining an OOS result without realizing it when working with an unchanged acceptance zone. To illustrate that risk, the additional measurement uncertainty has been added, reaching further into the acceptance zone (see Figure 3). Moreover, the full guard band should be considered now for narrowing the acceptance zone, as only the combination of documentary and pharmacopeial RS allows—theretically—for a congruent specification and acceptance zone. For the user, however, it is not possible to estimate how much narrowing of the acceptance zone is necessary.
To calculate the extension of the guard bands for a secondary RS, the candidate material for the secondary RS would first take the place of the substance tested and have an expanded uncertainty of 0.8%(w/w). Following the approaches outlined (see Methods) for Surrogatine HCl, and assuming an RSD of 0.2% for the method, an assay result of a substance tested with the secondary RS would then have a combined standard uncertainty of 0.48%(w/w), and an additional contribution of 0.08%(w/w) would be realized. In Equation 13, for simplicity, the assay value for S, the secondary RS, was assumed to be the same as for P in Equation 11. The guard bands would widen, from 0.80 to 0.96%(w/w), in agreement with the expanded uncertainties. Consequently, the acceptance zone should be narrowed down by 0.16%(w/w) on both sides.

\[
u_{c}(ST(R,S)) = \sqrt{S^2u_{c2}^2 + R^2u_{c3}^2} = \sqrt{96.19^2 \times 0.0028^2 + 1^2 \times 0.40^2} \approx 0.48\% (w/w)
\]

[Eq.13]

Depending on the precision of the chromatographic methods used for the comparison, the scenario can change to the better or the worse. As mentioned above, an RSD of 0.2% is realistic, but larger RSD (and lower) are also possible. Table III shows guard bands as expanded uncertainty results for RSDs from 0.2 to 0.5% for Surrogatine HCl. Inevitably, the guard bands widen with transition from pharmacopeial to secondary RS; they also widen with increasing measurement RSD.

**CONCLUSION**

As noted in the Discussion section, a significant change in the uncertainties of reportable values can clearly be seen between the pharmacopeial and secondary RS. The guard bands principle illustrates this in an evocative way. When applying the principle on the topic of secondary RS in quality control (QC) release testing, the range of acceptance/rejection zones will change, as the use of the secondary RS introduces an additional measurement uncertainty.

Although the authors do not intend to take a position on the appropriateness of the use of secondary RS in individual circumstances, consider two important facts:

- Assigned values of secondary RS inherently carry a larger measurement uncertainty, compared to primary (pharmacopeial) RS, as an additional measurement step is taken (8). Consequently, measurements obtained with the secondary RS carry larger uncertainties as well, compared to measurements with the corresponding pharmacopeial RS.

- It is inappropriate to work with certain acceptance criteria when using documentary standard (monograph) and pharmacopeial RS, and to work with the same acceptance criteria when using a secondary RS derived from comparison with the pharmacopeial one. In fact, the users of secondary RS should narrow down the original acceptance zone to ensure they would still be within specification limits of the monograph for their acceptance decisions.

The authors understand that it is difficult for users to assess the impact that the switch from pharmacopeial RS to secondary RS would have on the acceptance criteria, because uncertainties for pharmacopeial RS are usually not provided, for the reasons discussed previously.

To address this issue, the pharmaceutical QC community could opt to:

- Work exclusively with pharmacopeial RS when compliance through combination of pharmacopeial documentary and RS is established.

- Establish the identity of the secondary RS against pharmacopeial RS. The assay value and related measurement uncertainty should be determined independently for the secondary RS, using mass balance calculation instead of assay against the pharmacopeial RS. Acceptance zones should be adapted according to the measurement uncertainties found. This approach is practiced.

---

**Figure 3.** Schematic acceptance and rejection zones for Surrogatine HCl, combination of documentary standard (DS) and secondary reference standard (RS) compared to the pharmacopeial RS. Acceptance, specification, rejection, and guard band (g) zones are not true to scale; only uncertainties for characterization of the primary/secondary RS and assay result of substance tested have been considered.
in the pharmaceutical community (15) as suggested by a WHO expert committee (16). The results obtained with pharmacopeial and secondary RS should be compared; based on the comparison, the secondary RS can be released. Regular checks should be considered as to whether the relation is still valid, for example, during lot changes of the pharmacopeial RS.

ACKNOWLEDGEMENTS
The authors thank Dr. Ed Gump, Dr. Jeff Moore, and Dr. If-faaz Salahudeen of USP for their immensely valuable input during the revision phase.

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A pharmaceutical product can take many years to move from drug discovery to approval. Starting in research and development (R&D), significant amounts of data and process information are collected. This information is generated by many departments, each of which may operate in a silo. While the results of the process design are shared, often the underlying data are not, resulting in a loss of knowledge continuity and suboptimal tech transfer.

This problem and other related issues can be addressed through the intelligent application of advanced analytics software to coordinate data sharing and insights between teams and functional areas. This article will explore some examples of how such an analytics application can be used to support knowledge capture and collaboration, from the lab to the commercial manufacturing site.

Gaps in the flow of knowledge
As a drug moves into preclinical and clinical trials, the development team verifies that the process can scale to pilot and ultimately to commercial manufacturing, all without changes to critical process parameters that could impact product quality.

Pilot-scale data are usually stored in a process historian and compared to laboratory or process analytical technology (PAT) data, which are typically available as disparate data sources. As a result, it is often difficult to directly compare the pilot data to R&D studies. Disparate data sets must be extracted from their respective sources, then the data must be aligned before performing analysis. After this data wrangling, a retrospective analysis of scalability is performed.

Finally, if the product makes it through all phases of clinical trials and gets the stamp of approval from the United States Food and Drug Administration or another agency, it enters commercial manufacturing, where the recipe and process setpoints are transferred to internal manufacturing sites or to external contract manufacturers. Failure modes for process safety and quality are evaluated using cause and effect analysis, but for the most part, the manufacturing site is starting from scratch to collect data for process efficiency improvements.

In the event of a process deviation, R&D staff may be contacted for additional information on a particular failure mode, but commercial-scale manufacturers are largely unable to mine data or knowledge from the entire development process.

By the time a manufacturing deviation occurs, R&D scientists may have moved on to other projects, so the process to get materials, set up analytical methods, and provide additional information is inefficient. There is also an opportunity loss when R&D personnel are not able to work on new products because they must investigate issues with older projects. Despite these difficulties, it is critical to find the root cause of a deviation to prevent repeat deviations.

Data connectivity, integrity, and auditing
To support analyses across all stages of drug development and manufacturing, subject matter experts (SMEs) must be able to easily access data across a product’s full lifecycle so laboratory, pilot, and commercial manufacturing can perform comparable analyses and utilize the knowledge captured in tech transfer. It is crucial to minimize time spent cleansing and aligning data sets so these experts can speed time to insights. By connecting these disparate data sets to an analytics application, scientists, developers, and manufacturers can quickly find, explore, quantify, and document results about their processes to support tech transfer.

Data connectivity alone, however, isn’t enough, as data integrity is also of prime importance to guarantee safe and effective drug production. Information security considerations for authentication and authorization are necessary to ensure only designated individuals can access the system and interact with the appropriate data.
Tracking changes to calculations created in an analytics application is another key factor for regulatory compliance. Data administrators must be able to provide evidence that data are used properly, especially when making decisions for releasing a production run or changing parameters during manufacturing.

To support these types of efforts, companies must establish a designated good manufacturing practice (GMP) computing environment to use for production decisions. This environment may be an entirely separate system with its own connections to the data sources. Or, it may exist within the system used for engineering, as long as the system has access control settings to limit user edits of validated data, along with the ability to keep an audit log of changes made to calculations and other analytics configurations.

In either case, standard operating procedures and user permissions are leveraged to maintain the integrity of the GMP content and to provide SMEs with a different workspace in which to iterate through in-progress analyses.

Therefore, advanced analytics applications must provide secure connectivity to live, streaming, validated data, with controls for traceability and auditing. Calculations must be transparent and reproducible to provide easy understanding of exactly how the underlying data were processed.

Preparing for commercial manufacturing

Advanced analytics applications improve knowledge capture to support the technology transfer process by making experimental information available to commercial manufacturing personnel and other departments. Knowledge transfer is maximized by connecting to data sources at R&D, pilot, and manufacturing scale to overlay experiments with batches, and by providing tools to capture in-depth process learnings during scale-up.

In an example of a continuous twin-screw granulation process, an advanced analytics application was used to analyze the data from a design of experiments and to build a quality-by-design (QbD) multivariate design space around the process for ultimate use in commercial manufacturing. This model was developed by cleansing the experimental data to align upstream and downstream process signals in time, and then limiting the model inputs to steady-state operation.

These inputs were used in a multivariate regression model to determine the influence on critical quality attributes. The multivariate QbD model was then deployed in commercial manufacturing to provide a monitoring view of the process, flagging deviations from the defined quality specifications as they occurred to allow quick remediation (see Figure 1).

Continued process verification through statistical control charting

By proactively monitoring manufacturing processes, pharmaceutical companies can control variation to ensure quality product. Statistical control charting is used to support continued process verification (CPV), ensuring that processes are executed in a correct and consistent manner.

Control limits will change based on which product recipe is being run at the manufacturing site. It is therefore important to identify both the parameter to monitor and the associated product campaigns so statistical values for averages and standard deviation limits can be calculated for each product, as shown, for example, in Figure 2. After creating the sigma limits, run rules can be applied to search for process excursions, and for trends that may provide early excursion warnings.

Once the logic is defined for the CPV control charts and desired run rules, it can be applied to any period of time, or even be performed online to track batch variations in near real-time.

Ongoing process monitoring

To support the pharmaceutical tech transfer process, SMEs must be able to connect to data from many different process, lab, maintenance, and manufacturing sources to perform analyses. Once these

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Figure 1. Design space models applied to production data for ongoing process monitoring. Periods of deviation are automatically captured for reporting and further analysis.

Figure 2. Statistical control chart showing process variation and run rules.
Countering Counterfeiters and Diverters
Anticounterfeiting technology protects the supply chain from manufacturer to patient.

The never-ending battle against counterfeit pharmaceutical products has become fiercer with the pandemic. With product protection a constant concern, the market for anticounterfeiting technologies is strong, regulatory efforts are ongoing, and authentication and anticounterfeiting technologies are evolving. As a result, the anticounterfeiting packaging market is projected to grow at a 7.8% compound annual growth rate to US$189.9 billion (£138 billion) in 2026 (1). A major driver for this growth is the expanding use of e-commerce platforms, which make it easy to set up shop to sell fraudulent products and are largely unregulated. A study by Local Circles noted that approximately 20% of all products sold on e-commerce sites are counterfeit (1).

Anticounterfeiting laws and regulations, such as the European Union’s Falsified Medicine Directive and the United States Drug Supply Chain Security Act (DSCSA), safeguard prescription drugs available from pharmacies. “However, pharmaceutical manufacturers should be aware that these measures alone will not guarantee a product’s integrity and authenticity,” says Gene Dul, president of Schreiner MediPharm US. He says, “Only additional counterfeit-proof authenticity features can provide a comprehensive approach against fraud, misuse, and tampering.”

Unfortunately, the coronavirus pandemic has increased the opportunities for counterfeiting. “In a survey issued by IDC in June 2020, 70% of companies agreed that their supply chain is ‘very vulnerable’ to suffering more problems if the COVID-19 crisis lasted more than a couple of months longer, and 75% of companies agreed that the COVID-19 pandemic has ‘greatly increased/will greatly increase’ problems with diversion, theft, and counterfeiting of critical products such as test kits, vaccines, and antivirals,” reports Aimee Genzler, vice-president, Corporate & Brand Communications at TraceLink, the study sponsor (2).

In fact, in anticipation of a spike in counterfeiting, the US Immigration and Customs Enforcement Homeland Security Investigations (HSI) has launched Operation Stolen Promise 2, to halt the production, distribution, and sale of illicit COVID-19 treatments and vaccines. HSI reported that its agents have seized illicit proceeds and goods, made arrests, and shut down fraudulent websites (3), including the seizure of two domain names in December 2020 (4).

The proliferation of counterfeit goods stems in part from the shift to e-commerce, which has been accelerated by stay-at-home orders and advisories and reduced access to physical retail pharmacies. “The emergence of on-line pharmacies poses a significant threat of escalation in counterfeit pharmaceuticals and underscores the urgent need for on-dose countermeasures,” reports Peter Wong, chief operating officer at TruTag Technologies, which recently entered a partnership with Colorcon to provide advanced security coatings for on-dose use.

“Counterfeiters are opportunistic,” explains John Pitts, key account manager for Antares Vision, noting, “COVID-19 provided the ‘perfect storm’ for the counterfeiters: panic in consumers; product shortages from the brand name ethical providers; desire and, in many cases, requirement to purchase via e-commerce; and lack of and often conflicting information from the media and authorities.”

Joe Farrell, life sciences expert at Loftware, conurs, "It seems clear that whenever there are high-value pharmaceutical products, there will be people trying to profit illegally. The fact that the COVID-19 vaccines need to be shipped in stringent cold storage containers with radio frequency identification (RFID) temperature sensors along with specialized transportation methods will make it more difficult for counterfeiters to enter the supply chain, but not impossible.”

With COVID-19 vaccines now rolling out in limited quantities, demand will outstrip supply in the coming months.

Hallie Forcinio is packaging editor at Pharmaceutical Technology Europe, editorhal@sbcglobal.net.
“This will create a ripe environment for unscrupulous parties to offer fake product,” says Wong, noting, “Distribution of the COVID-19 vaccine is designed to go to many more points of dispensing than for a normal pharmaceutical drug, as governments seek to deliver vaccinations broadly and as quickly as possible while maintaining demanding cold-chain requirements. These logistical requirements will create higher than normal transition points in the overall supply chain, which in turn create increased opportunities for diversion, adulteration, and fake product to reach the patient.”

Counterfeiting countermeasures

The pharmaceutical industry has been on the leading edge of anticounterfeiting and brand protection efforts for many years. “Anticounterfeit solutions are usually tailor-made according to the needs of the brand owner,” says Paavo Sillanpää, senior business manager, Pharma at UPM Raflatac.

A diverse strategy considering threat scenario and product is needed. “Most pharma companies have a multi-layered approach,” notes Farrell. The most common physical solutions are tamper-evident labels and packaging materials, designs that prevent the placement of a counterfeit product into the original packaging, serialization, and overt and covert authentication methods such as holograms, invisible markers, and taggants. “Ideally, multi-level security concepts should be used that are individually tailored to a specific use case, combining analog and digital features, which can be verified by different stakeholders within the supply chain,” says Dul.

There is heightened interest in tools and technologies that go beyond the package to protect patients, such as on-dose solutions. In addition, says Wong, "the industry is increasing its public awareness campaigns of the problem of fake and unsafe medicine in an effort to educate consumers about the dangers of unauthentic drug products.”

As a result, Pitts predicts an increased focus on consumer engagement. He notes, “Enabling the end consumer and the dispenser to authenticate their products is powerful on so many levels. It makes counterfeiting more difficult, provides vital and real-time data to the consumer, and can offer the manufacturer feedback.”

Labelling technologies

Labelling plays an important role in the fight against counterfeit products. As the passport for moving products through the global supply chain, it contains any track-and-trace or authentication information. “In the label business, we have seen an increased interest in various tamper-evident (TE) solutions and holograms,” reports Sillanpää. One new product from UPM Raflatac combines heat resistance, advanced adhesion, and conformability. Designed primarily for the European market where cartoned blister packaging is common, the heat-resistant TE label won’t shrink in heat tunnels used to produce multipacks.

UPM Raflatac has also introduced sustainable TE labelling. It’s produced from Forest Film, which Sillanpää says is “the world’s first wood-based plastic labelling material.” Benefits include performance equivalent to traditional plastic film label materials and the ability to help pharmaceutical brands achieve sustainability goals.

Demand for more sustainable products extends to RFID and near-field communication (NFC) tags. Eco-friendly RFID and NFC tags from Identiv feature paper-based transponder inlays that reduce polyethylene terephthalate content, resulting in a repulpable substrate (5). RFID technology is integral to the Cap-Lock plus RFID cap adapter and label combination from Schreiner MediPharm. The label-integrated RFID inlay provides digital proof of integrity and first-opening evidence for syringes as well as product authentication. Dul explains, “The adapter is placed on top of the syringe’s primary closure and interlinked with it to equalize the diameter differences of the syringe body and closure. The label wraps around the syringe body and cap adapter and—once opened—provides irreversible tamper evidence due to an integrated perforation.”

Printing and tagging technologies

Magnetic ink is another potential anticounterfeiting tool. Technology from Inspectron relies on a proprietary reader, track-and-trace software, and magnetic ink, long used on checks to facilitate automated sorting. The magnetic ink is used to print a barcode, which is detectable even if it’s not visible to the eye. That means the code, which may be serialized, can be hidden on the inside of a carton or under a label and still be read. The current reader works from a distance of up to 2 mm, but units with longer read ranges are under development. “However, longer read ranges require bigger codes,” notes Nathalie Muller, head of innovation at Inspectron. Although the first commercial application of the technology inkjets the codes on paper to enable identification of diverted product, Muller says, the permanent magnetic codes could be printed on plastic or glass containers and potentially support tasks like vial tracking. Also under development is a hybrid one- and two-dimensional barcode that would hold more data.

On-dose technology enables authentication at the product level. Edible microparticles coupled with the Smart Medicine solution from TruTag Technologies confirms product authenticity and can help boost patient adherence and outcomes. A new Pharma Mobile App allows patients to scan each dose with their smartphone, authenticate it, and record that it was taken. If desired, the record of the dose can be shared with healthcare providers. The system also can link to other product information.
In April 2020, the US Food and Drug Administration accepted molecular tagging technology from Applied DNA Sciences into its Emerging Technology Program (6). The company says that its technology is a multilayered platform that gives both the dose and the packaging an immutable identity for authentication.

On 30 Nov. 2020, AlpVision launched its Alpvision COVID-19 initiative to protect COVID-19-related therapeutics and vaccines against counterfeiting. Under the programme, AlpVision provides pharmaceutical companies and their suppliers with the tools to deploy its Cryptoglyph digital security feature on their packaging. Invisible to the human eye, the Cryptoglyph feature can be authenticated via smartphone. Adopting the technology does not change the production process or involve additional consumables. In addition, the smartphone applications connect to AlpVision’s Brand Monitoring System, a centralized server platform that enables real-time monitoring of product authentication activities. AlpVision plans to provide this service for free until the World Health Organization declares the pandemic has ended (7).

Software tools
Physical technologies are common anticounterfeiting tools, but counterfeit and diversion prevention also relies on software. Farrell reports, “At Loftware, we are being asked for help in getting the correct information onto the label. It’s important to have an enterprise labelling solution that integrates with a company’s sources of data to make sure the correct approved information is automatically applied to the labels. This includes languages, barcodes, regulatory symbology, and regional product information. You also need a labelling solution that can aid with approving, managing, and promoting electronic information for use [data] to help speed the process for a faster time to market for these critical products.” Although not specifically an anticounterfeiting product, Software Spectrum software integrates with serialization solutions and ensures labelling is consistent, accurate, and contains the right serialized data and barcodes.

“The use of global templates in an enterprise solution also helps our life sciences customers to globally standardize on the look of their supply chain labels to help identify counterfeited products,” he explains.

The scalable Track My Way platform from Antares Vision offers single-unit, batch, and custom traceability; provides direct consumer engagement; and can extend from raw materials tracking to end-of-life package disposal/recycling. Geolocation functionality can track the harvesting of the raw materials, packaging locations, the movement of products through the supply chain, and the point-of-sale location.

In April 2020, TraceLink released an anticounterfeiting tool called Smart Distribution Tracking. By integrating the Internet of Things with product serialization, Smart Distribution Tracking provides full track-and-trace visibility for the secure delivery of vaccines, test kits, and high-value products.

Another software tool, the Summit Authentication Platform from Microtrace Solutions, is a customized system consisting of a self-authenticating, encrypted barcode; a Spectral Taggart; and a handheld detector plus a smartphone mobile app. “Our Spectral Taggart is a chemistry formulated into an ink that, when printed, is a highly secure ‘signature’ or ‘fingerprint,’” explains Brian Brogger, president at Microtrace Solutions. This signature can be authenticated instantly via the handheld spectrometer or smartphone without an Internet connection. For vaccines and therapeutics, the barcode and Spectral Taggart can be applied to security labels. The mobile app is then able to verify that the barcode has not been copied. The system also can provide real-time reporting and analysis.

The latest release of the Systech Brand Protection Suite from Systech International, the software solutions division of Markem-Imaje, delivers a fully integrated solution to combat counterfeiters, identifies product diversion, meets regulatory compliance, and provides analytics. The centrepiece of the suite, the company’s non-additive e-Fingerprint technology, turns any existing barcode into a unique, digital identifier to provide end-to-end visibility and actionable information as a product moves through the supply chain. New functions include the ability to push unique responses and content to users and smartphone authentication of e-Fingerprinted products. Responses can be tailored to the user, location, time, and safety of the product, and include photos or other information.

A new analytics platform, Systech Insight, offers a series of Information on Demand dashboards and an analytics data pool (8).

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deficits, and it’s classified as a category 1 carcinogen,” he says. “The biologic half-life of cadmium in the kidney is estimated to be between six to 38 years, and between four and 19 years in the liver (1). These half-lives reflect the fact that humans do not have effective elimination pathways for a number of toxic metals which have no known biologic function in humans. Excessive bioaccumulation is therefore regarded as potentially toxic and every effort must be made to analyse and limit patient exposure.”

“Raw materials used for chemical synthesis can contain traces of elemental impurities based on their production or origin source,” adds Johannes Hesper, product manager, Spectroscopy, Shimadzu Europe. “Catalysts and filters may release inorganic ions, and surfaces of tube reactors may react to a very low extent with the synthesis products. Additional risks are changes in ion strength and pH of synthesis media as often occurs during the process. Last but not least, formulation and packing can introduce impurities into the final pharmaceutical products.”

For biopharmaceuticals in particular, any materials that potentially come into contact with the final product should be inert, Hesper confirms. “Metal ions may interact with or covalently bond to the molecular structure [of the drug], replacing standard counter ions,” he says. “In the worst case, [the metals] are transferred into the human body where they can negatively influence the normal metabolism pathways.”

Sources of impurities
According to regulatory guidance, there are two sources of elemental impurities, explains Paul Kippax, Pharmaceutical Sector director at Malvern Panalytical, which are either intentionally added impurities or non-intentionally added ones. For the former, impurities could enter the drug product via the use of catalysts in the synthesis of APIs, for example. Non-intentionally added impurities can include contaminants from naturally sourced materials or from manufacturing equipment, dose container systems, or water used in drug manufacturing or formulation.

“Several potentially toxic metals, such as palladium and rhodium, are used as catalysts or reagents in the synthesis of APIs and must be removed to limit patient exposure,” notes Daniel Ingles, technical leader for trace elements, Metrics. “Other metals, such as lead and cadmium, are not commonly encountered in pharmaceutical products but are controlled because they accumulate in patients over time.”

Taking cadmium as an example, which is known to be toxic, Ingles iterates the necessity of the analysis and removal of trace metals in pharmaceuticals. ”Cadmium toxicity is associated with liver and kidney injury, osteoporosis, skeletal deformations, neurological

Regulatory requirements
In recent years, regulatory requirements for elemental impurity testing have been adapted and harmonized (2,3), and manufacturers are expected to demonstrate compliance via validated instrumental methods. “The most significant change in recent years is the withdrawal of the wet chemistry method for determination of heavy
metals from all regulatory guidance,” states Ferencz. “Elemental impurities testing must now be performed using validated instrumental methods to ensure proper exposure limits are met.”

“For nearly a century, heavy metals were controlled using a benchtop wet chemistry procedure, of which the US Pharmacopeia (USP), European Pharmacopoeia (Ph. Eur.), British Pharmacopoeia (BP), and Japanese Pharmacopoeia (JP) had similar versions,” Ingles reveals. “The assumption was that any metals that formed an insoluble sulphide would respond to it. Unfortunately, in practice, it was not effective in detecting heavy metals at concentrations of interest to modern industry and was gradually phased out and replaced by more technologically advanced methodologies.”

Currently, drug manufacturers are required to demonstrate compliance with the International Council for Harmonization’s guidance—ICH Q3D (4)—and USP’s guidance—USP <232> (5), Kippax highlights. Additionally, USP <233> outlines which analytical procedures may be used for the detection of elemental impurities (6), he adds:

“ICH Q3D sets out the harmonized requirements for detection of 24 elemental impurities, depending on whether these are intentionally or unintentionally added to a product. These limits are based on an understanding of the bioavailability of each element,” Kippax says. “USP <232> sets the maximum permissible daily exposure (PDE) for elements, again based on an assessment of their bioavailability. In general, the guidance provided is harmonized with ICH Q3D, except for total parenteral nutrition (TPN) products.”

Hesper stresses that regulations around the detection of elemental impurities are updated frequently. “Thanks to modern detection technologies and methods, the limits of detection are getting lower and lower,” he notes. “New studies on the effects of such impurities trigger reconsiderations of risks and limits.”

“The elemental impurities themselves are well defined, the exposure limits are under constant review by various governing and regulatory bodies,” concurs Ferencz. “There have been efforts to harmonize these limits internationally, but several regulatory agencies still choose to set their own levels based on alternative guidance.”

In terms of potential future updates, Ferencz reports that there have been several pushes to introduce separate limits for additional exposure pathways.

“While drug introduction techniques have been expanding, the guidance has not, and parenteral now covers a large range of introduction techniques that do not necessarily have the same exposure risks for the various elemental impurities,” he says. “As more research is done on organ specific effects of different elements, the pressure for this [regulatory update] will increase.”

“Based on the actual push in terms of biopharmaceuticals, especially due to vaccine development, regulations on limits for metal contamination could again be under discussion to avoid influences on final products by metal ions,” adds Hesper. “As processes for release and approval of new pharmaceuticals and vaccines are getting shorter and faster, it becomes more important to reduce possible risks to a minimum.”

**Commonly used techniques**

The most commonly used techniques to analyze elemental impurities is inductively coupled plasma–mass spectrometry (ICP–MS) or inductively coupled plasma–optical emission spectroscopy (ICP–OES). “Both techniques use a high energy plasma to ionize any elements present in the sample preparation and detect them using elemental masses or elemental emission bands,” Ferencz states.

“The advantage of using ICP is that it can detect a wide range of elemental impurities at very low concentrations,” confirms Kippax. “This [capability] enables the product safety requirements for the main product types (oral solid dose, inhaled, and injectable products) to be assessed.”

**In recent years, regulatory requirements for elemental impurity testing have been adapted and harmonized.**

Hesper concurs that ICP–MS is a robust and highly sensitive method used for trace analysis of heavy metals and adds that ICP–atomic emission spectroscopy (ICP–AES) has the ability to quickly analyze multiple elements in a large concentration range. “Of some use regarding elemental impurities is atomic absorption spectroscopy (AAS) for quantitative and qualitative analysis of many elements mostly in aqueous solutions and solids,” he says. “Rarely applied to the detection of elemental impurities is energy dispersive X-ray fluorescence spectroscopy (ED–XRF), which can analyze toxic elements in solid and liquid samples with high sensitivity.”

**Some limitations**

Even though ICP–MS is required to reach the desired levels of sensitivity, there are some limitations to the technique, according to Ingles. “The instrumentation is expensive and requires a trained analyst to operate it,” he says. “Additionally, there are technical complications in the analysis of arsenic and the digestion of nearly insoluble oxides of silicon and titanium.”

Although, it is possible to mitigate the complications with ICP–MS or ICP–OES through the use of appropriate sample preparation and background correction techniques, the cost and operation remains a barrier to businesses and leads to outsourcing, Ingles continues.
Another issue with ICP is that the sample preparation can be a lengthy process, asserts Kippax. “In addition, the preparation route, which involves sample digestion and dilution, requires a high degree of training,” he says. “As a result, although the method is routinely used in batch release, it is more difficult to apply during process development, where more rapid feedback and the application of quality-by-design (QbD) aids with process optimization and the development of a realistic process design space.”

There is also the possibility of gaining false positive results when using ICP–MS, as some elements have different isotopes with the same mass to charge relationship, Hesper highlights. “But, basically, all 24 elements of the ICH classes can be analyzed using the ICP–MS technique,” he notes. “Gold, mercury, and osmium can sometimes be challenging. If the focus [of the analysis] is only on the seven most toxic elements, AAS can be the method of choice.”

A major limitation, as is the case with any instrumentation, can be sensitivity, stresses Ferencz. “Methods must balance matrix effects with detection limits to properly monitor for the elemental impurities at the required levels,” he says. “The other major limitation of these techniques is speciation. Because ICP requires the atomization and ionization of elements for analysis, it cannot provide the information about the valence states and molecular forms of the elements.”

Ferencz explains that even though speciation can be relatively more commonplace for certain elements, such as arsenic and mercury, for other elements it is still a niche technique. “As pharmaceutical companies experiment with the use of different elements, especially transition metals, in novel molecules and biologic therapies, there is a growing need to quickly and accurately assess whether the element exists free in the toxic elemental form or properly bound in the clinically proven novel product,” he asserts.

The next step

“In the future, species analysis may become more important,” reveals Hesper. For example, if an analyst is seeking to differentiate chromium III/VI rather than simply measuring total chromium, then liquid chromatography (LC) coupled with ICP–MS is more interesting, he states.

The use of chromatography was also key for the future for Ferencz, who believes that the next shift in elemental impurities analysis will be the use of high-performance liquid chromatography (HPLC) coupled with ICP–MS. “The ability to separate and speciate all elements in a drug product allows for a more thorough risk assessment, especially as studies continue to prove the marked difference in toxicity between free elements and various bound states,” he notes. “This technique is still only used for very specific novel drug products, but as the market grows, it will move to be the technique of choice.”

When considering the practical issues that are associated with ICP-based methods, Kippax asserts that XRF, which offers a faster turnaround of samples, cost efficiencies, and simpler measurement workflows, is starting to be more widely adopted. He explains that there are two main areas in which XRF provides the greatest advantages—in-process development and quality control (QC) screening.

“XRF is applied to guide process development scientists toward effective elemental scavenging processes, providing rapid feedback on the capabilities of the process,” Kippax says. “This [application] can speed the time to release of candidate batches. In this mode of use, ICP may be used as validation that a realistic endpoint is achieved, ensuring that the concentration of impurities within the final dosage will be within specification.”

In QC screening, XRF can be applied in the manufacturing process to track the elemental concentration, Kippax continues. “For some pharmaceutical products, this may be sufficient to meet ICH Q3D or USP <232> requirements, depending on the product dosing regimen,” he says. “Where XRF is unable to meet the requirements for detection, it can provide information on the general concentration of elements within a sample—this can then guide sample preparation for ICP, avoiding measurement failures caused by the elemental concentration within the sample being too low or too high.”

However, Ingles states that, despite the technique being useful in the detection of a variety of metals, there are significant cost and operation barriers to the implementation of XRF in the pharmaceutical industry. “Alternative techniques more commonly adopted in the agriculture and food sectors may at some point be considered for pharma, they include AAS, atomic emission fluorescence spectrometry (AES/AFS), neutron activation analysis (NAA), and anodic stripping voltammetry (AVS),” he says. “As mentioned earlier, the techniques will need to meet ICH and USP reference requirements. There will also need to be a good use case to move away from the current, widely accepted approach.”

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Continued Innovation is Key for COVID-19 Recovery

More work is needed to educate businesses on the value of innovation and the availability of funding.

Luke Hamm is CEO of GovGrant

According to the Federation of Small Businesses (FSB), more than a quarter of a million businesses are due to close their doors for the final time in 2021 (1). The COVID-19 pandemic has ravaged many businesses across the United Kingdom, and as we navigate the third lockdown it is still unclear what lies around the corner. Thinking ahead, therefore, may seem impossible. However, for the tables to turn, businesses must adopt an open-minded approach that balances surviving the here and now, with working towards long-term, sustainable recovery solutions.

As we seek to build back better from the impacts of the pandemic and bolster the strength of the UK as a nation independent of the European Union, the healthcare sector has a prime opportunity to boost innovation through the prioritization of targeted R&D and the commercialization of intellectual property (IP), which will be critical driving forces behind achieving this resilience.

However, what has become even more apparent in the second half of 2020 and early 2021, is the nation-wide misunderstanding and underappreciation of such readily available solutions. The government has been right to prioritize the sectors most at risk and make large sums available at a time of need; however, throwing more money at businesses where the funds are just swallowed up and the payback may be minimal is simply not going to achieve the recovery we need.

Keeping it within our borders

While innovation, in this instance, has been key in providing us with the crucial answers we need and giving us all hope that there is some light at the end of the tunnel, it’s also vitally important for our hopes of a sustainable economic recovery. A big part of this comes down to keeping R&D and innovation on UK shores. Historically, R&D was largely a domestic process in the UK (2), but the development of automation technologies and cheap offshore labour has resulted in many companies moving production overseas.

This trend has continued apace since first emerging in the late 1980s as cost-saving became the driving force behind global sourcing, driving manufacturers towards lower cost regions, typically in Asia. Unfortunately, a large proportion of the development work has followed suit, reducing the investment in UK-based innovation in recent years.

But as important as encouraging innovation on UK shores is, it becomes a pointless activity if IP isn’t being commercialized in the way it should be. For example, every pound spent now on R&D and innovation will hold its value in 20 years in terms of company value. Her Majesty’s Revenue and Customs (HMRC’s) data that highlights the disparity in spending on R&D and Patent Box is proof that the hard work of businesses is not being followed through to the patent stage, meaning all commercial value is lost (3).

A key reason behind Switzerland leading the way in the World Intellectual Property Organization’s 2020 Global Innovation Index for 10 consecutive years (4) is due to its excellent innovation outcomes including patent applications, IP receipts, and high-tech manufacturing products.

Utilizing IP

Put simply, the UK needs to take a leaf from Switzerland’s book and focus on how we can turn the UK into an IP powerhouse. A key factor to businesses surviving and thriving in a post-pandemic world will be a company’s ability to find and maintain its unique selling point—something even more important in the healthcare sector. Indeed, patents are vital to the healthcare industry and for fostering healthcare research. Without the patenting system, new innovation would undoubtedly slow significantly.

However, there is confusion around one of the primary purposes of IP—value creation. The majority see IP as something they need to protect and defend rather than commercialize.
Pandemic Response

Leading by example

For the health sector in particular, innovation is at the forefront of the response to COVID-19 that will help drive recovery from the pandemic. At GovGrant, our recent research found 86% of UK small-to-medium enterprises (SMEs) in the health sector think innovation is important for the recovery from COVID-19 (1), and rightly so. Whilst the headlines rightly laud the progress of AstraZeneca in the development of the ‘Oxford vaccine’, it would be remiss to assume it is game, set, and match for innovation in the UK health sector. Despite AstraZeneca’s part in what has undoubtedly been a game-changer in battling COVID-19, innovation in a complex field such as healthcare is not always a matter of introducing new drugs, treatments, or technologies. In fact, innovation is happening every day, up and down the country—but it is not always recognized. Furthermore, just because vaccines are in production, does not mean the opportunity to innovate is gone for the health sector. Big steps such as treatments and cures are rightly celebrated, but so too should be improvements to processes, products, or business structures to name a few. GovGrant’s research found 46% of UK SMEs in health sectors said the biggest barrier in the way of R&D activity was the lack of opportunity to innovate, perhaps reflecting the fact SMEs only view ground-breaking inventions as ‘innovative’ (1).

Indeed, the development of COVID vaccines has only heightened the scope for innovation for businesses of all sizes. After all, collaboration was at the centre of vaccine development if we look at the German SME, BioNTech, in collaboration with pharmaceutical heavyweight, Pfizer, similar to AstraZeneca’s work alongside the University of Oxford.

While questions remain over logistics, distribution, and, and, perhaps most significantly, cost of the vaccine as a result, this distribution is one example of the importance of continued innovation. The ability to effectively distribute AstraZeneca’s vaccine around the world could make a big difference in how effectively we are able to combat not just COVID-19 but also the threat from future viruses.

Reference


—Luke Hamm

Research from GovGrant reaffirms this, with less than a quarter of UK small-to-medium enterprises (SMEs) claiming that the primary purpose of a patent was to gain commercial value, while more (38%) thought the primary purpose of a patent was to protect innovations (5). To a business, an IP right should be driven by how they can improve margin, sell more, or engage better with potential clients.

The majority see intellectual property as something they need to protect and defend rather than commercialize.

The government’s motivation behind the Patent-Box scheme is to help retain IP in the UK, by encouraging businesses to undertake R&D activity within its borders rather than offshoring. However, as innovation within the healthcare industry develops, the correct use of IP will become key, particularly with the challenges of recovery from COVID-19 and Brexit looming on the horizon. Businesses need to start thinking about IP from a commercial perspective, rather than just protection—after all, it’s value that will drive investment into the UK as a whole.

Solutions are available

It is clear more needs to be done to educate businesses around the value of innovation, while demonstrating the availability of funding through schemes readily available, and already baked into the budget such as the R&D tax credit scheme and Patent Box. There is value for everyone—tax credits provide businesses with an immediate cash boost in return for their hard work, while fuelling further innovation and driving longer-term growth for both the businesses and the economy. Indeed, an assessment made by HMRC shows the R&D tax credit scheme can accurately show return on investment (6).

Similarly, Patent Box exists to reward businesses financially for those keeping R&D within the UK, but is still under-utilized. Data from HMRC in 2020 showed that while £5.3 billion (£5.9 billion) was claimed in R&D tax credits in 2017-2018, only £1.1 million (€1.2 million) was claimed under the Patent Box scheme, proving IP is not being commercialized in the way it should be (7). Encouragingly, GovGrant’s research demonstrates that 76% of healthcare, 78% of medtech, and 82% of pharmaceutical SMEs are aware that the government offers the R&D tax credit and Patent Box schemes to incentivize R&D and when used effectively, can alleviate the cost of innovation for SMEs—something cited as a barrier to innovation, with 47% of those in health-related sectors claiming cost is hindering efforts to innovate (5).

However, with so many still concerned about the cost, there is clearly a disconnect between the support on offer and if it is enough. So, this is the wake-up call. The tax office is so often overlooked as a mean for supporting businesses—but it is an essential way to distribute much needed funds available in appropriate and fair proportions. Businesses willing to invest more receive more, therefore
It is high time for the government, industry bodies, and businesses to work together to [invest funds] more effectively.

It is, therefore, high time for the government, industry bodies, and businesses alike to work together to create a butterfly effect that transcends across the UK, so that as we continue to navigate the crisis, funds being thrown at businesses that merely paper over the cracks can be invested more effectively elsewhere. And instead, the government can focus its efforts on creating an environment where innovation can thrive, driving the sustainable recovery we need to achieve.

We’re all in this together—and amidst the devastation caused by COVID-19, we’ve been given an opportunity to change our fortunes for the long-term. But we need to act now.

References
5. GovGrant, “Innovation Nation—The UK

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data are collected, engineers and scientists can calculate statistical limits, key process indicators, and aggregations using analytics tools. Important trends and metrics can then be assembled into static batch reports or live updating dashboards for ongoing process monitoring. These dashboards can continue to update and include the latest data for monitoring the process in near real-time.

These dashboards and reports promote knowledge capture and collaboration across organizations by bringing together multiple analyses, often configured by a team of process experts. These reports can be reviewed by operators, engineers, and managers to ensure each batch is progressing within the limits specified during the drug development and pilot scale-up processes. Using the digital tools that make data visible across the product lifecycle, any observed deviations can be analyzed against lab data to search for similar issues and learnings.

Conclusion
Throughout the product lifecycle, substantial knowledge is gathered about the process through R&D experiments and scale-up batches. Advanced analytics applications enable rapid and more effective tech transfer throughout the product lifecycle to shorten the time required for handoffs between departments within an organization.

During tech transfer, advanced analytics applications can help researchers understand the relationships among variables and determine critical process parameters at laboratory scale, as well as verify scalability and optimize the process as it moves into pilot production. In addition, these learnings can prove critical for monitoring process variability and quality, and for performing deviation investigations at commercial scale.

Advanced analytics applications thus empower SMEs to document their analyses, capture information, and mine previous information from colleagues to speed up the process development timeline and improve efficiency at commercial scale.

Figure 2. Statistical control chart with averages (light blue center lines), 1 sigma (blue lines), 2 sigma (yellow lines), and upper and lower limits (red lines) calculated for four different product types.
Frequently Asked Questions on Regulatory Inspections

Experts Steven J. Lynn, executive vice-president, Pharmaceuticals for Regulatory Compliance Associates, Inc., and Susan J. Schniepp, distinguished fellow for Regulatory Compliance Associates, Inc., provide simple answers to frequently asked questions regarding regulatory inspections, although many of the concepts can be applied to internal and supplier audits as well.

Q. What documentation should I have ready to present to the inspectors?
A. There are a number of documents and supporting evidence that can be staged prior to an inspection whether it is in-person or is being handled remotely. The objective is to make the inspection process go smoothly for both parties. At a minimum, there should be a list of all current standard operating procedures (SOPs) provided to the auditor so they can choose the specific ones they are interested in reviewing, a listing of customer complaints for the past two years, a list of current closed and open deviations and corrective and preventive actions (CAPAs) for the past two years and the site’s quality manual, the current organizational charts, a copy of the employee training programme, and a map of the facility. In addition, it is advisable to have a short introductory presentation (5–10 minutes) that describes the facility, the products produced, and the operating hours of the facility. This information can be provided up front for the inspectors.

Q. How long should an inspection/audit take?
A. There really isn’t a defined time frame to answer the questions. Questions that can be answered immediately should be answered immediately. Questions that need a little more investigation or clarification before answering should be responded to in a timely manner.

Let’s look at an example. If the inspector is reviewing a technical document, they may ask to see a previous version of the document. If this document is stored off site, then it may take a day or two to retrieve it. This is acceptable as long as you inform the inspector why there is a delay in providing the requested information. Bottom line, all questions and documentation should be answered as soon as possible, and if there is a delay, it is important to be transparent with the inspector and explain the reason for the delay.

Q. If an inspector makes an observation, do I need to have a corrective action in place before the inspection ends?
A. No, there is no reason to have a corrective action in place before the inspection ends. In some cases, the observation may be easily corrected, so it might be possible to have the corrective action in place before the conclusion of the inspection, and if the correction is acceptable to the inspector, it may actually help remove that observation from the final inspection report. Having said that, the best advice is to wait until the inspection is completed before you implement any corrective action so you can be sure the action is appropriate for the observation and you have had time to make sure related documentation and activities have also been updated in relation to the observation.

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