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‘Polling’ All the Way

As the UK heads to the polls for an unusual December general election, industry issues manifestos on medicines while Europe rejoices some movement … finally.

Much along the same lines, the UK BioIndustry Association (BIA) released its biotech manifesto that has called on the next government to also commit to R&D investment, maintain medicines regulations post-Brexit, and improve patient accessibility to medicines. “The UK life-sciences sector is creating innovative therapies and medicines for patients, and supporting hundreds of thousands of jobs across the country. This general election is an opportunity for political parties to back this exciting sector, which contributes billions of pounds to the UK economy and delivers life-saving and life-enhancing medicines for patients,” said Steve Bates OBE, chief executive of BIA in a press release (7).

For the manufacturers’ organization, Make UK, the future agreement between the UK and EU is of overriding importance. “The first and foremost priority for the next government must be an agreement with the EU that also passes through parliament as soon as possible, which removes ‘no deal’ and ensures four key outcomes to safeguard the future prospects for manufacturers,” said Stephen Phipson, chief executive of Make UK in a press release (8).

Brexit taking centre stage
As to be expected, Brexit has been the primary issue on the lips of every election campaigner. The Conservatives, with Boris Johnson at the helm, want to leave the EU with the deal negotiated earlier in the year. Jeremy Corbyn and Labour are aiming for a ‘softer’ Brexit deal and a second referendum. Whereas, Jo Swinson, leader for the Liberal Democrats, hopes to scrap Brexit altogether. And these candidates represent just the three of the parties in the house of commons.

With numerous smaller parties also taking parliamentary seats up and down the country, there is a strong likelihood of a hung parliament, that could see many variances on the Brexit scenario for 2020 and beyond. So, there may yet be a ‘cold, cold Brexmas’ on the horizon as the future relationship of the UK and EU very aptly ‘hangs’ in the balance.

Industry manifestos
The Association of the British Pharmaceutical Industry (ABPI) issued its manifesto in mid-November 2019, highlighting three main themes that the industry body believes will be integral for the UK’s life-science sector (3). These themes are ensuring the UK is the top place for patients to access cutting-edge medicines and vaccines in the world, securing the future UK-European Union (EU) relationship, and building on R&D investment.

“The next government will shape one of our country’s most valuable assets: an incredible pharmaceutical industry that employs tens of thousands and invests billions in research,” said Mike Thompson, chief executive of ABPI, in a press release (6). ”We don’t just want NHS patients to get the latest breakthroughs; we want the UK to continue being home to the science that makes them possible, with all the global investment that comes with it.”

As the UK heads to the polls for an unusual December general election, industry issues manifestos on medicines while Europe rejoices some movement … finally.

Not since 1923 has the general public of the United Kingdom been sent to the polling stations in the month of December (1). However, the wish of the current UK prime minister, Boris Johnson, to hold a general election a mere two weeks before Christmas (12 December 2019), has been accepted and passed through both houses of parliament (2).

This decision was taken with the hope of overcoming the stalemate surrounding Brexit. During the campaign trails, bio/pharma industry bodies launched their own manifestos, aimed at ensuring sufficient support for the industry body manifestos on medicines while Europe rejoices some movement … finally.

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Felicity Thomas
Editor of Pharmaceutical Technology Europe
FThomas@mhhgroup.com

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The Challenges for Regulators in the Digital Age

Regulators are facing huge challenges on how to deal with the digitalization transformation occurring in the healthcare and pharmaceutical sectors.

Digitalization is spreading rapidly throughout Europe’s healthcare and pharmaceutical sectors. But the pace of the change is leaving regulators struggling to keep up. Vast amounts of data from the development and production of medicines and patient treatments and outcomes are being collected, processed, and analyzed for creating algorithms for application in artificial intelligence (AI) such as machine learning.

However, few pieces of legislation in Europe, even at the national level, specifically tackle the problems emerging from the digitalization transformation in healthcare, such as quality of data and lack of standards.

**Regulatory issues with digitalization**

Regulatory issues with digitalization are mainly focused on three, often overlapping, areas. First, there is AI itself, which is an umbrella term used to cover technologies enabling machines to perform tasks such as recognition of specific images and patterns in datasets.

Algorithms, the step-by-step instructions given to AI equipment to process data or conduct tests, pose regulatory challenges because they can be ‘trained’ to draw up their own instructions or make their own decisions. In pharmaceuticals and related European sectors, the use of AI, and other digitalization tools, is mainly confined to applications at the points of patient care. It has yet to penetrate deeply into medicine production and even drugs R&D. But this is expected to change over the next decade, mainly because of the growth in personalized medicine, which will lead to an overlap between drug manufacturing and point-of-care treatments in, for example, hospitals.

A survey in 2017 of executives in life sciences, including pharma, by Camelot AG, a German-based management consultancy, found digitalization was having zero impact on manufacturing and only five percent impact on drug development and clinical trials (1). However, by 2020 the executives expected the impact on manufacturing to increase to 21% and on R&D to 11%, while by the early 2030s it would have risen to 35% and 29%, respectively.

During the next decade, regulations of AI will be playing a much bigger role in European pharma than it is now, with the biggest factor being the use of regulations to gain the trust of patients in the new digital technologies.

A report on AI, by the London-based thinktank Future Advocacy in conjunction with Wellcome Trust, a charitable foundation, predicted in 2018 that the biggest influence on social, political, and ethical aspects of AI centred on consent, fairness, and rights (2). Matters on rights also need to be considered when developing regulatory oversights of AI, the report said. Aspects of care being increasingly delivered autonomously by AI raised questions such as “do people have a right to know how much AI is used in their care?” Or “do people have a right not to have AI involved in their care at all?”, the report asked.

The European Union’s General Data Protection Regulation (GDPR), introduced in 2018 to replace the 1995 Data Protection Directive (3), enables individuals to have more control over their personal data in all sectors, including healthcare, even when it is exported outside Europe.

The legislation obliges controllers of personal data to take “appropriate technical and organizational measures” to implement the data protection principles. This and other provisions in GDPR have raised fears in the pharmaceutical industry, among others, that the regulation could stifle innovation.

One controversial protection in the legislation is the ‘right to explanation’, which entitles citizens to “fair and transparent processing” of their personal data as well as “meaningful information about the logic” used in automated decision-making systems (3). Lawyers and law academics believe, however, that because of the way the ‘right to explanation’ is written into the regulation it is not legally binding.

**Tailoring regulations required?**

In a report published in November 2019 on AI policy, Digital Europe, a Brussels-based trade association representing digital technology producers,
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recommended that AI regulation should be drawn up to meet specific needs (4). It suggests that policy makers should endeavour to use current regulatory and legislative frameworks as much as possible, with, if necessary, additional guidelines to make them more effective.

In the application of good manufacturing practice (GMP) in a digitalization age, regulators in Europe are relying on Annex 11 of the EU’s GMP guide, which covers computerized systems (5). At the core of the annex is the application of risk management throughout the lifecycle of the computerized system taking into account patient safety, data integrity, and product quality. “As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerized system,” the annex specified. Operators of plants using AI are as a result being considered to have the same capability to assess risks with AI as with other traditional computerized systems.

The Geneva-based Pharmaceutical Inspection Co-operation Scheme (PIC/S), whose members are regulatory authorities in the GMP field and whose GMP guide is virtually identical to the EU’s, has conceded that Annex 11 has become ‘outdated’.

Defining AI
One glaring gap in regulatory controls on AI is the lack of an internationally agreed definition of AI. A committee of the House of Lords of the UK parliament complained in a report on AI last year (2018) about participants in its hearing of evidence providing ‘dozens of different definitions’ (6).

The Paris-based Organization for Economic Co-operation and Development (OECD), representing the world’s rich nations and which was responsible for drawing up an international version of the principles of good laboratory practice (GLP) in the 1990s, announced in February 2019 that it is working on a set of AI guidelines that would include an answer to the question, “What is an AI system?”

The OECD’s committee on digital economy policy has made recommendations identifying a number of principles on responsible AI stewardship. These include fairness, transparency, explainability, robustness, safety, and accountability.

The Geneva-based International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC) do provide standards related to AI. But in healthcare, these mainly apply to medical devices or the hardware component of drug-device combinations (DDC).

A joint big data taskforce of the European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA) complained in a summary report issued in February 2019 about the lack of standards, particularly on data quality (7). The taskforce had been split up into six subgroups covering genomics and other ‘omics’, such as proteomics, clinical trials, adverse drug reactions, and other aspects of healthcare data. “Almost without exception, each of the subgroups raised the need for standardization as a key prerequisite” to drive data digitalization forward, the report said. Data standardization is needed to “define and, where possible, improve data quality and progress to actions to promote data sharing, access, and enable robust big data processing and analysis.”

Many datasets in Europe, outside of those for clinical trials, are not standardized because they have evolved over many years when different technologies have been applied to them. Nor were the data generated to support regulatory decision-making and hence the need to comply with strict quality guidelines.

Even with relatively new areas of science such as genomics on which data on almost 250 million genomes is available and relatively well structured, accessibility to the data is restricted because of lack of standardization, according to the report. Much of it is siloed by disease, institution, and country, generated with different methodologies, analyzed by non-standard software and often stored in incompatible file formats.

Regulators must have “the capability and capacity to analyze, interpret, and profit from the data generated,” the summary report said (7). “In this way, we will improve our decision making and enhance our (evidence-based) standards.”

One barrier could be a lack of specialized expertise among regulators in data science. This sort of knowledge is needed to enable “informed and critical assessment of regulatory applications in future” of innovative products and processes, according to the report (7).

The knowledge gaps may be so large that a system for linking up experts with regulators may be necessary to ensure that the capacity of the regulatory system to make appropriate assessments is maintained. Standardization of data will be a major challenge, which from the regulatory perspective will require prioritization of what issues need to be tackled first.

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Preventing Disruptions in Drug Supply Continuity

Communication and planning are crucial to recovering from supply, operations, and facility disruptions.

Agnes Shanley

As the pharmaceutical supply chain becomes more complex, potential vulnerabilities are increasing. Adding to the challenge are random and unpredictable supply disruptions caused by acts of violence, fires, floods, or natural disasters. Survival depends on understanding and collaborating with suppliers, customers, and insurance companies to manage risk, and ensuring that effective emergency response plans are in place. Without the right approach, the economic losses from inability to operate, product contamination, or loss of income can be devastating, says Frank Russo, founder and principal of Procor Solutions, LLC, a risk management and claims solutions consultancy.

Manufacturers that have been slow to develop strategies may soon get a push from regulators. The US Food and Drug Administration (FDA) has proposed requiring drug companies to conduct periodic risk assessments to identify and mitigate supply chain vulnerabilities (1). This legislative proposal is in President Trump’s fiscal year 2020 budget. Based on results of the assessment, companies would be required to have risk-mitigation plans, such as having redundant manufacturing capacity in place. FDA would use a risk-based approach to determine which companies would be required to do this. The agency plans to apply these requirements to drugs that are considered “life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery” (2). The requirements would apply to drugs that have been on the FDA drug shortage list within the past five years or that meet one or more criteria that increase the risk of shortage.

Some smaller companies may not have business continuity or crisis response plans in place. Overall, however, pharmaceutical companies are quite sophisticated about risk management when compared to companies in other industries, says Russo. He sees natural disasters, which have stepped up in frequency and severity over the past 15 years, as the industry’s top business continuity threat. Other problems are more frequent upstream outages that occur when key suppliers cannot ship APIs or other materials required to make the drug.

Often, these glitches occur because of quality and compliance problems (e.g., when regulators place a supplier’s facility on import ban) or result from accidents or other problems at supplier plants. “Given pharma’s complex and increasingly efficient just-in-time supply chains, these scenarios can be a recipe for disaster,” says Russo. “A minor calamity at a supplier’s plant can have a significant impact, interrupting production and revenues for extended
periods upstream, ultimately reaching the retail pharmacy level. Although specifics depend on the severity of each case, and the companies and products involved, a single blip can cost in the tens of millions of dollars if it lasts for too long without options for mitigation," he says.

**Ransomware and IT**

Cyberattacks and computer hacks are also a factor. Ransomware can make discussions with insurance companies difficult, says Russo, because these programmes are often installed well before they are detected. As a result, it can be hard to pinpoint when the company’s financial loss actually began, he says.

New pharmaceutical product launches also challenge manufacturers to quantify losses once a supply disruption occurs. "Without a history of revenues from that drug, companies may struggle to demonstrate lost income to insurers," he says. Therefore, they must document everything, have clear projections of product revenue from the start, and share that information with insurers, Russo says.

"Companies need to accurately and adequately convey what the loss was, one component at a time," he says. Russo recommends that companies maintain steady communication with their insurers. In order to ensure cash flow, it is better to request payment in installments rather than waiting to have the claim paid in full, he says.

A growing number of websites, applications, and other platforms are available to help companies better respond to crises and to sharpen their resiliency and business continuity efforts. One example that Russo cites is In Case of Crisis, a mobile application that helps teams communicate, share standard operating procedures (SOPs) and checklists, and file incident reports. Investing in risk mitigating technology will help speed recovery. Not only can it prevent damage to company assets, it can also reduce insurance costs, says Russo, as a growing number of insurers take a more holistic approach that considers the total cost of risk. Some insurers now offer discounts and other benefits to companies that invest in preventive technologies, for example Internet of Things water sensors that collect real-time data on plant equipment. "This kind of approach is becoming more common," says Russo.

In 2017, Hurricane Maria in Puerto Rico provided the ultimate test of pharmaceutical company emergency response and business continuity programmes. Companies that include Amgen, Johnson & Johnson (J&J), AbbVie, and Eli Lilly faced flooding and loss of power and communication systems. Most of the island was without power for months, with some areas enduring blackout conditions for almost one year; in some cases, companies were not able to locate some of their employees for several weeks.

Pharmaceutical manufacturers in Puerto Rico were equipped with diesel power generators, but many struggled with communication and network connectivity. Speeding data and IT system recovery after a major disaster demands careful planning and documentation well in advance, says IT consultant Orlando Lopez. Not only should all possible failures and risk scenarios be determined and written down, but their impacts should be carefully assessed and staff mobilized, he says. In addition, he says, alternative systems should be made available, and teams should be dedicated to handling corrective actions, troubleshooting, error diagnostics, and preventive actions.

"Procedures to be followed in case of failures and outages should be carefully described and documented, as should the system rebooting process after bugs have been fixed," says Lopez. The same goes for maintaining data that were first entered using alternative means (e.g., cell phones or paper) and later entered into computerized systems. Lopez notes that the National Institute of Standards and Technology’s (NIST’s) *Contingency Planning Guide for Federal Information Systems* can be very helpful in these efforts.

One lesson that emerged from the hurricane was the importance of testing the procedural controls used to restore computer systems after the storm struck, says Lopez, who notes the need to avoid a single point of failure by having diverse sites for recovering basic IT and communication functionalities.

**The duty of care**

In the end, the manufacturers continued to operate after a devastating storm. What may have enabled productivity was the fact that companies supported their staffs, some of whose homes had been damaged or destroyed by the storm or who had lost loved ones. This driving force, which risk and business continuity consultant Steve Goldman calls “the duty of care,” may ultimately be the key to business continuity. “At Amgen, one of our priorities is to prepare all our staff so they can manage a crisis event, not only from a business-continuity perspective but from a personal one,” says Arleen Paulino, the company’s senior vice-president of manufacturing. “Following Hurricane Maria, we mobilized resources to support our staff with pay continuity, access to food, water, showers, and laundry service as well as gas and generators. Their safety and well-being were our priority,” she says.

After the hurricane, Amgen was able to maintain supply to patients without misses or shortages, a fact that Paulino attributes to a robust business resiliency strategy that leverages investments that the company has made, not only in staff training and support, but in infrastructure, technology, inventory, diversification, and business continuity. Long before the storm hit, Amgen had already upgraded its sites on Puerto Rico so that they could withstand the force of a Category 5 hurricane. In addition, she says, staff...
had been trained and [crisis response] tools had been continuously tested to ensure that emergency plans would work as expected.

Inventory strategy was also crucial, Paulino says, and safety stocks helped ensure sufficient product supply, while back-up manufacturing locations relieved pressure, aiding recovery. A mindset of continuous improvement is essential for any business continuity strategy to work, says Paulino. “At Amgen, business continuity plans are tested constantly across the company,” she says, noting that internal critique sessions are crucial. “They help us better understand potential disaster scenarios in the future, and learn how we can be more effective,” she says.

When operations are running normally, it can be easy for companies to become complacent about keeping records updated, even for things as basic as organizational charts. At one customer facility, for instance, Goldman found that organizational contact lists included the names of people who had left the company or died. Another missing link for some manufacturers is any deep knowledge of their suppliers, and little regular communication with them. The automotive industry is a model for doing this right, says Russo, and proactive companies such as Johnson & Johnson and Amgen have adopted supply chain mapping, a tool first used in other industries, for pharma. Amgen began to explore the approach in 2011 after the tsunami in Japan, and began mapping in 2013, running a small pilot with close suppliers. Efforts have paid off so far, and by 2018, the company reported having visibility into all tier 1 suppliers and a large percentage of tier 2 suppliers, and even down to tier 3 in some cases (3).

At the highest level, management expectations and customer expectations will drive emergency response plan development, and each must be thoroughly documented, said Aaron Duff, global director of EHS process excellence and standardization at J&J, in a webcast hosted by Pharmaceutical Supply Chain Initiative (PSCI) in June 2019 (4). There must be alignment and agreement between the two sets of priorities if emergency response efforts are to succeed, he said.

On the ground, however, all utilities must be evaluated, including wastewater and fire wastewater operations, as well as electric power outage preparedness. One important detail with floods is determining in which direction the storm water will run, Duff said. Both engineering controls (e.g., fire or water-level emergency alarms) and administrative controls (e.g., staffing, and who has specific training) must be examined, Duff said in the webcast. Another crucial step is to communicate and develop a relationship with local emergency response organizations. “They should be involved in drills and training exercises. You don’t want to be meeting them for the first time when an emergency occurs,” he said.

Identifying high risk operations is then key, and examining any gaps between existing control measures and what will be needed to keep the facility safe. The next step is developing a risk matrix to define the severity and likelihood of the emergency occurring and designating a cross-functional crisis-management team of at least three people.

The team will need an incident commander, and training and drills should be scheduled at least once or twice a year, involving site management and staff as well as emergency responders and even government responders. Drills should be as rigorous as possible to simulate what people will experience during the actual event, says Goldman.

A formal written policy must be established for communicating with the public, says Goldman, in particular, a social media strategy geared to mobile phone users. He suggests that companies dedicate a website, and have several Facebook pages, a Twitter, and a LinkedIn account ready to go and that a dedicated team monitor and respond to comments on social media as the event unfolds.

Business continuity is becoming more prominent as a field, with some companies staffing at the vice president level, says Goldman. However, even the best strategy can be weakened by a disconnect between enterprise-level risk management and site-level efforts.

Breaking down silos
Silos may separate business continuity from enterprise risk management (ERM) teams, even though both involve the same stakeholders and both focus on risk. Experts note the need for a common language and for synchronizing efforts (5). Ideally, they say, data from business continuity exercises should be used to improve ERM activities, while key risks that have been identified by ERM teams should frame business continuity exercises.

Operations and Business Continuity teams should also work more closely together, says Goldman, but senior management support for business continuity is essential. “Risk is not a crisis response, it’s a probability of something happening, and once a disaster hits, it’s at 100%. In the end, it’s not so much what gets you into the crisis but how you deal with it that counts,” he says.

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Excipients are essential components of drug formulations. While physiologically inert, they have functionalities that achieve many formulation goals, such as API stabilization, taste masking, and extended release. “Functional excipients play an integral role in achieving the desired biological performance of many drug formulations,” asserts Robert Lee, president of the CDMO division of Lubrizol Life Science Health. Many excipients, however—depending on the API structure, dosage form, packaging configuration, and storage, handling, and use conditions—may also interact via mechanisms that negatively impact efficacy and safety. The challenge is to identify the right excipients for each formulation.

Many possible interactions
Interactions between excipients and APIs can occur via both chemical and physical mechanisms. “Many small-molecule APIs are inherently complex and have diverse functional groups that can undergo multiple reactions either simultaneously or in sequence,” says Anil Kane, executive director and global head of technical and scientific affairs with Thermo Fisher Scientific. Thus, the degradation of pharmaceuticals is an area that is complex.

The major mechanisms for chemical decomposition of pharmaceuticals with other excipients include hydrolysis, dehydration, oxidation, isomerization/epimerization, decarboxylation, dimerization, polymerization, and photolysis, according to Kane. Complexation with excipients to form salts is also possible.

In some cases, the excipient itself doesn’t initially interact in a negative manner with the API. For that to occur, it must first undergo a chemical reaction to generate a new species that can affect the API. For instance, Lee notes that some unsaturated polymers can in the presence of oxygen form peroxides that will degrade oxidatively labile APIs.

“While many pathways of degradation are obvious from basic organic chemistry principles, it is not uncommon to find surprising degradation chemistry leading to unexpected degradation products and pathways,” Kane observes.

Physical interactions include hydrophobic and hydrophilic media interaction and interactions that affect particle size and shape. For instance, in nanoparticulate suspensions, excipients physically adsorb to the surfaces of the API nanoparticles via steric or charge-charge interactions.

In fact, the dosage form plays a role in determining the potential interactions that can occur. Molecular mobility in solids is far less than in the liquid state, hence chemical reactivity in the solid state generally occurs under severe conditions of temperature and/or humidity or in presence of a catalyst, according to Kane. Considerations for chemical degradation are more critical for non-sterile oral liquids and sterile parenteral products because the excipients and APIs are more mobile and there are more opportunities for chemical reactions. For lyophilized products, interactions can occur in the initial buffered solution as well as in the lyophilized cake.

Desirable and undesirable impacts
Interactions between excipients can be either beneficial or harmful. Hydrophilic and hydrophobic media interactions are generally beneficial, according to Richard Shook, director of drug product technical services and business integration at Cambrex. “Through these mechanisms, polymers can delay the release of the drug substance to better target the site of absorption and protect the API from degradation in the gastrointestinal tract. Polymers can also be used to enable prolonged duration of API release, increasing the time of drug absorption and decreasing patient dosing frequency, thereby assisting treatment compliance,” he explains.

For example, lower-molecular-weight polymers assist in “bridging” of particles during wet granulation processing and can be used to coat API
the next stride in inhaled therapeutics...

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particles to increase their interface with surrounding media during dissolution. Higher-molecular-weight polymers, meanwhile, can form hydrogels that restrict the release of API, enabling extended release. Preferential polymer bridging between smaller and larger particles during wet granulation, meanwhile, can affect particle size and shape selection, leading to desirable granule formation. Saturated fat-based lubricants such as magnesium stearate and stearic acid can create a hydrophobic barrier within the dosage form to ensure proper delivery.

For nanoparticulate suspensions, which offer increased dissolution rates and potential higher bioavailability due to the high surface area of the particles, the high-energy milling process used to create the nanoparticles generates crystals with high surface energies. Use of excipients to lower the surface energy and stabilize the nanoparticles is therefore necessary, according to Lee. Polymeric stabilizers such as polyvinyl pyrrolidone provide steric stabilization, while charged excipients such as sodium lauryl sulfate participate in electrostatic interactions.

APIs containing aromatic groups can, in some cases, benefit from interactions with polymeric excipients that also possess aromatic functionalities, according to Lee. In this case, there is the potential for the aromatic rings to stack together (π-π stacking), which may lead to stabilization of the API.

Some chemical reactions are also desirable. For instance, Shook points to the use of pH-enhancing excipients such as citric acid, sodium hydroxide, etc., which can stabilize pH-sensitive APIs by creating microenvironments within dosage forms. Alternatively, certain excipients can be added to participate in competitive reactions as a means of protecting the API. One example is butylated hydroxytoluene, which in some formulations is preferentially oxidized over the API.

When interactions of the API with functional excipients lead to degradation and the formation of known or unknown impurities, however, the results are generally not beneficial. In these cases, the interactions can have a number of consequences, such as physical changes including discoloration, agglomeration, plug formation, precipitation, cloudiness in liquids, etc., according to Kane.

One of the most important undesirable reactions is the Maillard reaction between amines and alcohol functionalities, the latter of which are common in sugar excipients such as lactose. The result is formation of high-molecular-weight brown polymeric material with a strong aroma, leading to formulations that are discoloured and have an unpleasant odour, according to Shook. Another common issue is the degradation of pH-sensitive APIs due to exposure to acidic or basic environments. In some cases, encapsulation can protect APIs that are hydrolytically or enzymatically labile, Lee notes.

“The main impact of the interactions of APIs and excipients, however, is not only loss of potency and the intended therapeutic efficacy, but also formation of degradation products that may or may not be toxic,” he observes. “Degradation of the API will result in a drug product not meeting specifications for its assay (or potency) and content uniformity. The dissolution performance of the active drug substance may also decrease. Thus, the drug product will not meet its expected critical quality attributes,” he continues.

**Chemical functionality must be understood**

With efforts to reduce time and cost to market, the potential for stability issues increases dramatically, according to Kane. The ability to rapidly predict and assess the potential for stability and safety concerns is, therefore, an important part of speeding the development of innovative drug therapies. “Degradation prediction enables understanding of labile functionalities critical in designing less reactive, more stable analogs, and degradation studies conducted by a chemistry-guided, predictive, stability approach enable analysts to deliver stability-indicating methodology more efficiently,” he asserts.

The first step is to examine the possible mechanisms of chemical decomposition for the API in the context of the common functional groups that are present in the molecule. APIs containing functional groups, such as ionizable moieties, amines, and carboxylic acids, present the greatest risk for interacting with excipients, according to Lee. Excipients that can enhance these mechanisms should be avoided.

In addition, it is important, according to Kane, to consider the excipient impurity profile, which is generally lot specific. Impurities of concern include water, solvents, metals, acidic/basic compounds, and reactive molecules (e.g., peroxides, aldehydes, organic acids). The amorphous content is an additional factor, as is the equilibrium moisture content and hygroscopicity profile, effective pH in water, and the thermal and thermal/humidity solid-state stability (chemical and physical).

It is worth noting, adds Lee, that in some cases, excipient suppliers offer special, extremely high-purity versions of certain products. When an API is identified as being susceptible to oxidation, for instance, “cleaner” excipients with very low limits of oxidizing substances would be preferred as a means for reducing the risk of undesirable interactions.

**Characterization of interactions is essential**

The choice of excipients is usually based on forced degradation data for the API. “Forced degradation data provide information about the potential degradation pathways for the API and for the formation of impurities in acidic and basic environments, when exposed to light or oxidative conditions, and under high temperature and high humidity conditions,” he says.
Proper characterization of excipient/drug substance interactions using physical and chemical testing is paramount, Shook agrees. “No stone should be left unturned when identifying critical material attributes of a target drug substance. For example, various excipient compatibility studies, such as binary blends, formulated prototypes, compressed versus loose powder, etc., can be designed to align with the available API and timeline,” he observes. The studies, he adds, are best employed in a phase-appropriate manner.

Prior to initiation of any compatibility studies, a thorough review of relevant drug substance information available at the time of the compatibility studies is extremely important, according to Kane. This evaluation should include a review of the structural understanding of the molecular scaffold and the sites of known reactivity, a detailed review of the synthetic route, a review of the API solution state stability data (pH, thermal, and photostability challenges), any and all forced degradation data, and metabolite formation information and output from predictive models of degradation.

“A risk-assessment approach should be used that involves combining the knowledge of reactive impurities in excipients along with an understanding of the potential degradation pathways for the API. Other factors such as the drug-to-excipient ratio, crystal form of the API, environmental conditions, surface acidity, and microenvironmental pH must also be considered during the assessment and mitigation of risk. Finally, mitigation strategies should include ‘designing out’ the incompatibilities through formulation design, packaging configurations, or through establishment of a control strategy,” Kane comments.

**Formulation and packaging strategies**

There are a number of strategies that can be employed to minimize undesirable excipient-API interactions ranging from avoidance of problematic excipients to the use of excipients that stabilize or protect APIs, devices that physically separate formulation ingredients until the time of administration, and packaging that incorporates chemical agents that inhibit certain chemical reactions.

For oral solid-dosage forms, there are several different options for protecting APIs that are sensitive to moisture or oxidative degradation. In the former case, Kane notes that excipients with low moisture content should be used to reduce the probability of chemical interaction due to hydrolysis and silica should be added to adsorb any moisture picked up in the formulation. Moisture-barrier film coatings can also be employed, according to Shook. Inclusion of desiccant packs in the drug product bottle pack and/or flushing an inert gas such as nitrogen or dry air during packaging are also recommended.

For APIs that can react with oxygen, excipients that contain or can generate peroxides should be avoided, while antioxidants should be added to the formulation in the optimal quantity, according to Kane. Selection of the right packaging components and reducing the headspace of the pack may help prevent exposure of the product to an oxidative environment. Inclusion of oxygen scavengers in the bottle pack and blistering and/or bottling the drug product under inert atmosphere (dry air or nitrogen) is also recommended to improve the stability of a packaged product.

When dealing with fat-based lubricants such as magnesium stearate and stearic acid, proper characterization of material blending is important, according to Shook. “Blending times must be optimized to balance proper introduction of the lubricant with minimal coating of the drug substance particles,” he says.

For non-sterile oral liquids and liquid injectables, the addition of acidic or basic excipients or buffering agents as appropriate can help maintain the desired pH and prevent degradation of the API, according to Kane. If an excipient is necessary to achieve proper delivery but cannot be in contact with the API for extended periods of time, the use of dual-chamber syringes or packaging in separate vials are options for keeping the ingredients physically separate until the time of administration, according to Lee. “The key for these solutions is to have a good understanding of the length of time during which the combined ingredients will be stable in order to ensure that patients are being administered the correct formulation,” he comments.

**Question every excipient**

Whichever solutions are chosen, they are selected based on extensive pre-formulation and analytical work and intended to provide design control that will lead to acceptable products, according to Lee.

Most importantly, Lee stresses that it is essential to make certain that each excipient used in a formulation has a well-defined function. “It is critical to question every excipient that is added to a formulation. Formulators must be able to justify the use of each and every excipient in their formulations, and ensure that they are using the minimal quantity for each that will afford the target product profile,” he asserts.

To achieve that goal requires experience and expertise in formulation development and the potential physical and chemical mechanisms of interaction between excipients and APIs with a wide range of functionalities.

“The best strategy to prevent future drug substance and excipient interaction headaches is to partner with an experienced, proactive formulation team,” says Shook.

“Strong collaboration between a formulation team and an analytical team conducting forced degradation on the drug substance can also prove highly beneficial,” he concludes.
Tackling Solubility in Drug Development

Spray drying is a versatile and rapid technique that can provide companies with a suitable and scalable option to improve the solubility and bioavailability of drug products.

Felicity Thomas

The proportion of poorly soluble molecules entering the drug development pipeline is increasing year-on-year, raising the bar for pharmaceutical companies in terms of how best to approach the challenge of improving solubility and bioavailability. “Over the past 20 years, drug development pipelines have been filled with drugs that present solubility issues,” confirms Márcio Temtem, site manager, R&D Services, Hovione. “It is estimated (1,2) that the current proportion of poorly soluble compounds in the development pipeline is between 70% and 90%.

Where APIs have poor solubility, this has a marked effect on a drug’s efficacy within the body and can lead to poor absorption, poor bioavailability, and increased pharmacokinetic variability,” adds William Wei Lim Chin, technical specialist, Science and Technology, Catalent. “Since many of these drugs exist as crystalline materials, one approach to improve the API’s performance is to create an amorphous solid dispersion (ASD), for which spray drying technology is a key part of the manufacturing process.”

An approach with merit

“Solubility, bioavailability, and stability are some of the most difficult formulation challenges faced by the pharmaceutical industry at present, and spray drying offers a very suitable solution,” explains Manuel Leal, business development director, Idifarma. “The process involves spraying a solution or suspension that contains the excipient and active substance inside a drying chamber. Dry particles are dispersed and collected by a cyclone as the solvent is evaporated at high speed. The ASDs with different particle sizes obtained after spray drying achieve better solubility than the API alone.”

The rates of spraying and evaporation in spray drying are crucial, according to Chin, who notes that evaporation must take place before either crystallization or phase separation has time to occur. “Amorphous forms are intrinsically more soluble than crystalline materials, as there is no crystalline lattice energy to be overcome,” he says. “Spray drying also gives a finely divided powder that can be processed into any dosage form that can incorporate powders, including capsules and tablets.”

Adding to Chin’s point, Temtem notes that the flexibility afforded by spray drying is a clear advantage of the technique over others that are currently available. “Spray drying enables development across a broad range of drug delivery options,” he says. “Additionally, as it is a flash drying process, it can be applied to many different molecules, such as those that have a thermally labile character, as the drug product will not be exposed to the high temperatures itself.”

There are significant benefits of spray drying, specifies Leal. “As is the case with many common technologies, batch size is not limited by the equipment capacity as spray drying operates on a continuous production process, which can be easily re-run. This scalability means that spray drying represents a swift, cost-effective solution,” he confirms.

“Another advantage spray drying has is in the formulation of products that have unusual or difficult characteristics,” continues Chin. “Products that may be sticky or hygroscopic, slow to crystallize, or difficult to isolate are all good candidates for spray drying.”

For Temtem, one of the most important advantages of spray drying over other techniques is that process development can be achieved using minimum quantities of materials. “For example,” he continues, “comparing with other available technologies, it is possible to perform process development with just a few grams of materials with spray drying, whereas to get the same information with other techniques, such as hot-melt extrusion or co-precipitation, you would potentially need from hundreds of grams to kilos of material. This is a big advantage, particularly in the processing of new chemical entities where API availability is limited.”
Multiple applications
“The quality achieved through spray drying a powder can influence the drug’s preparation downstream and how it is administered to patients,” explains Chin. “For example, particle engineering by spray-drying enables further development for inhaled delivery, which is the cornerstone in the management of patients across a spectrum of respiratory diseases.”

Concurring, Temtem also notes the increased traction that is being seen in the field of inhalation. “Spray drying is particularly beneficial in the preparation of composite particles for inhalation, both from a product stability and product performance perspective. During the spray drying process, ingredients are combined at the molecular level, improving the stability of the API and adjusting the cohesive-adhesive balance of the materials,” he says.

“The advantages of spray drying can be applicable to multiple drug products, from over-the-counter to prescription, and in a wide variety of therapeutic areas,” adds Leal. “One therapeutic area that can reap the advantages of spray drying is oncology. By altering the pharmaceutical form of the final product, spray drying can facilitate different administration routes. If solubility of a drug substance can be improved and the route of administration can be changed from injection to oral, then patient compliance and quality of life will also be positively impacted, he confirms.

“In antibodies, protein, and vaccine therapies, the drug substance is usually in a liquid state,” asserts Chin. “To improve its stability and to have the flexibility to administer it via dosage routes other than injectable and oral suspension, a spray dried powder offers many advantages and can be manufactured into conventional oral solid dose forms, which are more acceptable to patients with chronic diseases.”

Furthermore, as more companies are looking to tackle more rare disease areas and are approaching drug development and approval via the fast track or breakthrough regulatory programmes, spray drying can provide an enabling option, emphasizes Temtem. “For instance, by employing spray drying combined with modelling, for both product and process development, it is possible to accelerate the development lifecycle significantly, while also improving the drug’s performance.”

An attractive investment choice
The broad applications and ability of spray drying to improve solubility have made it an attractive choice for investment by companies and outsourcing partners throughout the industry. “As the industry struggles to find new drugs that improve existing therapies, the need for more innovative processes to advance the galenic formulation of a finished product has become essential,” states Leal. “As spray drying can achieve this, it has naturally become one of the top investment choices for many companies focusing on complex development projects.”

“Identifying a suitable dispersion technique is not necessarily easy, but the benefits it offers in terms of scalability of manufacture and dose form development has led to spray drying becoming a crucial tool within a formulator’s toolkit,” adds Chin. However, Chin iterates that industry has also experienced issues in the development of spray-dried formulations as a result of a lack of capacity at the commercial scale. “This issue has been addressed by some contract development and manufacturing organizations (CDMOs) investing in additional capacity,” he says.

The move towards fast-track programmes and breakthrough therapies is also driving investment in spray drying, states Temtem, echoing his earlier thoughts. “The ability to move quickly through the development lifecycle is critical for companies at the moment,” he says. “Spray drying has clear advantages to help in the area of time efficiencies, and as a consequence, the number of programmes using spray drying as a technique are increasing exponentially.”

Trends driving adoption
“Both versatility and speed are driving adoption of spray drying techniques,” says Chin. “The technique offers versatile formulation options and flexible downstream dose form manufacturing into tablets, powder-filled capsules, and inhaled drug products. It is a highly scalable process too, that allows for precision control of particle engineering, including particle size, bulk density, the degree of crystallinity, and levels of both organic volatile impurities and residual solvents.”

The ability to enhance the physical properties of drug products, particularly when looking at the ability to change parenterally delivered products to those that can be administered orally or by inhalation, will also lead to greater adoption by the industry of spray drying. “It’s important for the industry to continue to support patient adherence by looking for ways to improve comfort such as offering products in forms that patients can take at home,” adds Leal.

For Temtem, the combination of spray drying and drug productivity will become more prominent in the future, along with continuous manufacturing in the downstream processing, both of which will enable accelerated development. “Additionally, another trend for the future is the use of Big Data and the associated digital transformation. With a simple click of a button, it will be possible to gain information about the most adequate process conditions for a molecule, and when combined with empirical and mechanistic modelling, [Big Data and digital transformation] will also be able to speed up development,” he adds.

“Speed and agility are key to what comes next in the area of spray drying.”

References
Peer-Review Research

Approaches to Reduced Sampling and Testing for Starting Materials

Christian Rack

This article discusses reduced sampling and testing of starting materials or components. Different strategies are presented to reduce the workload at the steps from sampling to release. Viewpoints from the different pharmacopoeias and regulatory authorities, as well as selected literature, are reviewed.

Pharmaceutical manufacturers must ensure the quality, safety, and efficacy of their products (1). Examples in the past showed the importance of starting material testing for the quality of the finished product. Unidentified impurities in starting materials, at times, have led to serious harm or even death of patients (2,3,4).

An essential prerequisite for any analysis is that the sample is representative of the quality of the whole batch (5). A non-representative sample will lead to incorrect assumptions about the quality of the starting material, because it does not truly reflect the characteristics of the lot being sampled (6). The steps from goods receipt to release of the starting material are summarized in Figure 1.

Even though quality and other regulatory requirements are mandatory, economic aspects are important as well. When reduced sampling and reduced testing are considered, intelligent approaches fulfill both aspects (7).

The aim of this article is to give an overview of the viewpoints from different pharmacopoeias and authorities on reduced sampling and testing. The viewpoints are complemented by selected literature. Furthermore, different strategies are discussed to reduce the workload at the steps from sampling to release. The focus of the article is on starting materials or components. Table I provides clarification on terms used herein.

Sampling requirements
According to the European Union good manufacturing practice (GMP) guidelines, “the identity of the contents of each container of starting material” has to be assured (8). This requirement is specified by the European Commission (EC) EudraLex Volume 4, Annex 8, which says, “the identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample” (9).

According to Annex 8, it is permitted to deviate from this requirement. If it can be assured by a validated procedure that no container is labeled incorrectly, it is permitted to sample only a proportion of the containers. In addition to

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this, aspects such as the general GMP level, the manufacturing conditions, and the nature of the starting material and the finished drug product should be considered. The Swiss Medic published a technical interpretation that might be helpful for conducting such a validation. The approach involves a scrutinized look at the packaging and labelling process and to assess potential risks at the different process steps (14).

The reduction via validation is generally possible for starting materials coming from a single product plant or starting materials coming directly from a manufacturer. It is unlikely, however, that a validation could be successful for a starting material that is obtained from brokers or that is for parenteral use (9).

The US Food and Drug Administration (FDA) does not have strict requirements for the number of containers that must be sampled, but the number must be representative, and a scientifically sound sampling plan must be used (15, 16). Aspects like the variability of the material and the quality history of the supplier should be considered (17). ANSI/ASQ Z1.9-2003 for bulk and ANSI/ASQ Z1.4-2003 for discrete material are considered an appropriate standard for a sampling plan (18). An exemption is glycerol (19, 3). Here, FDA and the European Medicines Agency (EMA) share the expectation that some tests have to be performed on each container. It is not required to test those specifications on each container (9). Often, the square root + 1 sampling plan of the World Health Organization (WHO) is used for these purposes (22). But it should be considered that this plan is only one of three options and not WHO’s recommendation for the sampling of starting material. Therefore, the general usage of this plan is seen as critical by the authorities (23, 18).

The sampling for processing relevant parameters (e.g., water content or particle size distribution for solid oral dosage forms) has its own unique challenges. For each starting material, it must be evaluated if a sampling from different areas within the container is required, based on the possibility of an uneven distribution of the parameters. For the choice of the containers that should be sampled, a computer aided randomization is recommended (18).

### Table I: An overview of the different sampling and testing terms.

<table>
<thead>
<tr>
<th>Term</th>
<th>Where to find</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw material</td>
<td>International Council for Harmonization (ICH) Q7</td>
<td>A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs (10).</td>
</tr>
<tr>
<td>Starting material</td>
<td>Glossary European Union good manufacturing practice (GMP) guide</td>
<td>Any substance used in the production of a medicinal product, but excluding packaging materials (11).</td>
</tr>
<tr>
<td>Source material</td>
<td>ICH Q11</td>
<td>Cell banks are the starting point for manufacture of biotechnological drug substances and some biological drug substances (12).</td>
</tr>
<tr>
<td>Component</td>
<td>US 21 Code of Federal Regulations 210.3(b)(3)</td>
<td>Component means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product (13).</td>
</tr>
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</table>
Reduced sampling

Usage of alternative test methods. The European Pharmacopoeia (Ph.Eur) sets clear requirements about the identity testing of monographed substances. The identity tests described in the first identification may be used in all circumstances, whereas the second identification requires full traceability of the starting material to a batch certified to comply with the requirements of the monograph (24).

The usage of near-infrared spectroscopy (NIR) for pharmaceutical applications has been discussed since the late 1980s (25). The United States Pharmacopeia (USP) and Ph.Eur. list NIR and Raman spectroscopy as methods for identity testing (26–29). According to EMA, it is permissible to perform identity testing on a statistically representative composite sample when this is supplemented by NIR analysis on every container (30). For the validation of NIR analysis, detailed requirements are given (31, 32).

It is common practice to assess homogeneity via NIR and ensure identity via compendial methods. No guidance was found related to this practice. However, validation of either the direct identity testing or the homogeneity testing with subsequent identity testing requires similar approaches. Some cases in the past showed that the combination of NIR and the compendial methods was superior to the usage of only compendial methods (33).

According to the Q&A document of Health Canada, the identity of each container can be assessed by two approaches. First, every container is tested by a discriminating method, which may not necessarily be the monographed method. Second, the identity and the potency are tested on a composite sample (23).

Use of composite samples for identity testing. In general, it is required to perform identity testing on each container. EMA allows the use of composite samples for the identity testing, when the identity of each container is additionally assessed by NIR (30). FDA and Health Canada accept identity testing on composite samples under certain considerations. The main point is that the identity test is specific and selective to detect incorrectly labeled substances in a composite sample (17,20,23).

For glycerol, FDA and EMA require the testing of each container for identity and the limit test for diethylene glycol (19,3).

Reduction of sampling by choice of container size. A pragmatic approach to reduce the efforts for sampling for identity testing could be to increase the container size. As a consequence, fewer tests would be required for the same amount of starting material. However, this approach requires the assessment of potential other problems, such as handling or storage.

Preparation of the composite samples

According to Annex 8, it is permitted to use representative composite samples for purposes other than identity testing (9). But no details are given about how many samples of single containers can be combined in a composite sample. An idea can be found in the Q&A document from Health Canada. In the context of identity testing, a maximum of 10 containers can be mixed (23).

In general, the composite sample should be representative and homogenous. The procedure for the preparation of the composite sample should be described. It should be evaluated to see if the composite sample is homogenous.

USP describes the preparation of composite samples of powder starting material. If it is necessary to sample from different places within one container, the samples should not be composited (15,18).

Reduced testing/skip testing

The term “reduced testing” describes the practice whereby, after receipt of the starting material, not all parameters of the specification are tested. Only a reduced number of parameters are tested, while the other parameters are taken from the certificate of analysis from the manufacturer. This is an established approach in the pharmaceutical industry that requires an established system for the qualification of suppliers (34–37). The DIN ISO 2959-3 from the International Organization for Standardization (ISO) describes the statistical requirements for establishing this approach (38).

According to ICH Q6, reduced testing should not be established before the market authorization is granted (39). The prerequisite for reduced testing is an audited and qualified manufacturer that has been assessed and classified (34, 35, 36).

Some requirements in circumstances where reduced testing is permitted or minimum requirements are applicable can be found in different guidelines. According to chapter 5 of the EU-GMP guide, the manufacturer should have appropriate experience with the material (8). ICH Q7 requires full testing on at least three batches (10). Health Canada also recommends testing the first three batches of the starting material and repeating this procedure whenever the manufacturing process has changed (20). Some authors suggest testing the first 30–40 batches in full analysis (37).

The manufacturer of the medicinal product should establish the frequency for full testing. The accepted differences between the internally generated analytical results and the results of the supplier certificate of analysis should be defined, before the results are compared (35).

It is industry practice that at each starting material undergoes a full testing on an annual basis. According to Health Canada, it is permitted to do a rotational full testing if one manufacturer supplies more than one starting material. For example, if a manufacturer supplies three starting materials, it is possible to perform a full test on only one of the starting materials each year. At least every five years, a full testing of each starting material should be performed (20).

If the testing of the drug product manufacturer identifies a discrepancy in comparison with the starting material manufacturer, an investigation should be done first by the
As described in the previous sections, there are different options to reduce the sampling and testing of starting material. The market authorization holder has the ultimate responsibility to ensure the quality of the starting material, but the viewpoints of the different authorities could help to derive a strategy.

Sampling generally requires identity testing of each container. Reduced sampling is possible, but requires additional work to justify it. Independently, if the sampling for the full analysis is created from the samples of the identity testing or separately, a general square root +1 sampling plan might be too simple. A risk-based sampling plan is recommended. The identity testing of only mixed samples is possible under certain circumstances. The method used must be suitable to identify potential mix-ups even in mixed samples. In combination with a spectroscopic method, such as Raman or NIR, it is possible to perform the monographed or the approved methods on mixed samples.

The analysis for the full testing requires a representative and homogeneous mixed sample. The preparation of the mixed sample should be described in detail, especially the number of samples that are permitted to be combined in one sample.

A full testing of all parameters at every goods receipt is not required. Results from the manufacturer’s certificate of analyses can be used. However, it should be defined when it is permitted to move from full testing to reduced testing, at which frequency the full testing is repeated, and under which circumstances it is necessary to move back to full testing.

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Disclaimer
This article represents a personal view of the author and is not necessarily that of B.Braun.

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17. FDA, “How does FDA interpret the regulations (21 CFR part 211) regarding the establishment of expiry dating for chemicals, pharmaceutical and medicinal product manufacturer, and if he/she does not find the root cause, the investigation should be extended to the supplier/manufacturer of the starting material. Until completion of the measures, the certificate of analysis of the manufacturer should not be accepted (8).

Skip or periodic testing means that neither the manufacturer of the starting material, nor the pharmaceutical company test a certain parameter (37). If a pharmaceutical company wants to establish skip or periodic testing for a registered specification parameter, this approach must be submitted to the authorities (40, 41). In general, according to FDA, a required criteria cannot be not measured without a surrogate test (42). But for certain parameters (e.g., heavy metals or residual solvents), USP allows excipient manufacturers to perform skip testing, if validated processes are in place. This approach is also applicable for non-monographed excipients. However, full testing is required annually, and certain parameters, such as identity and strength, must be tested every time. The applied testing frequency of each parameter must be shown on the certificate of analysis (43).

In the end, it is the responsibility of the pharmaceutical manufacturer to verify if all necessary parameters have been tested. It is recommended to audit the suppliers and to verify the results from the manufacturer with results from in-house testing (43).

Discussion
As described in the previous sections, there are different options to reduce the sampling and testing of starting material. In combination with a spectroscopic method, such as Raman or NIR, it is possible to perform the monographed or the approved methods on mixed samples. In general, according to FDA, a required criteria cannot be not measured without a surrogate test (42).
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Visualization Enhances Facility Design

Can virtual reality unlock the biopharma manufacturing capacity challenge?

Nicole Fontourcy is head of Visualization Technology, Pall Corporation.

As we witness a health revolution with the development of biological medicines, biopharmaceutical companies are still facing major challenges around how to manufacture these drugs and get them to market as quickly and safely as possible.

The wide range of new and emerging product types, such as cell-based therapies, gene therapies, antibody-drug conjugates (ADCs), monoclonal and stripped-down antibodies, RNA interference drugs, and live microbe therapeutics, all require very different manufacturing capability and capacity than traditional pharmaceuticals. Moreover, as the biopharmaceutical industry comes of age, current blockbuster medicines are, or will soon go, off-patent. This means there is a growing need to also increase capacity to manufacture biosimilars.

Biopharmaceutical companies are continuously demanding new and improved bioprocessing technologies to reduce costs, increase efficiencies, and bring treatments to market faster. Year over year, companies spend and invest more on their R&D, new technologies, bioprocessing capacity, staff, and other infrastructure.

To meet the growing demand for manufacturing capacity and address the changing needs of an evolving industry, digital technologies are becoming increasingly important to biopharmaceutical manufacturing companies. One area of innovation is the virtual design of manufacturing facilities.

When constructing a new biomanufacturing facility, there is an ever-increasing number of bioprocessing options. Having to design, build, and operate a facility before knowing whether the right processes, equipment, and workflows have been chosen, adds considerable risk, especially given significant capital expenses. Advanced visualization, mixed reality (MR), and virtual reality (VR) tools are now being used to inform planning and implementation decisions and enable engineers and designers to plan a new facility, in minute detail, long before construction begins.

Simulation enables biopharmaceutical manufacturers to identify and resolve problems before they occur. It also creates an opportunity for those who will be working in the facility to virtually walk through the infrastructure: to understand the space, get used to the instrumentation arrangements, and build their knowledge of the full biomanufacturing process. They can identify any practical shortcomings and feed this back to those managing the design process, thus enabling them to select optimal instruments, tools, and processes to maximize uptime and gain efficiencies.

Using VR in facility design

Servier, an independent international pharmaceutical company, used a VR tool to design, plan, and implement one of its new biomanufacturing facilities. Pall and digital transformation specialists OUAT! worked together to develop the tool using a virtual simulation platform (HakoBio, Pall), which enabled Servier to design its new facility in a virtual, three-dimensional (3D) model at the start of the project.

The virtual facility was used to give the team a real sense of the layout and test whether there was sufficient space to safely and comfortably manipulate the equipment when needed. These tests allowed the designers and engineers to refine the design of the space and ensure that scientists and technicians would not be crowded when working in the space, such as when exchanging disposable, single-use components like bioreactors.

They also looked at how well the equipment would work in an end-to-end bioprocess. The virtual visualization was used to optimize the location of each piece of equipment and maximize usage over time by testing different configurations and combinations to find the best solution. A Gantt chart, for example, shows the output from a digital twin of a viral vector gene.
Manufacturing

therapy bioprocess. Spatial issues or bottlenecks could be identified, which would improve the overall uptime of each unit operation. Spatial issues are particularly critical for manufacturing suites that incorporate single-use systems, where the interconnectedness of each piece of equipment requires careful planning to fit most effectively with operator workflows.

Using this type of digital twin approach to fully visualize a future manufacturing facility, biopharmaceutical companies can find the best layout and use of equipment and optimize and reduce when possible the size of their overall facility. Supported by VR-based information, these decisions were made more quickly and earlier in the design process, avoiding potentially costly issues later and accelerating construction of both processes and facilities.

Tackling the skills shortage

There is a shortage of skilled staff in the biopharmaceutical industry, which is affecting current and future capacity and production. In 2017, more than 50% of bioprocessing facilities experienced capacity problems due to difficulties hiring certain operations staff (1). This demand for staff is set to increase as the biopharmaceutical industry continues to grow, despite the move toward more automation and single-use components.

Increasingly, VR and MR technologies are being used for training, providing employees with a 3D virtual space in which to learn and practice bioprocess design skills. Handling equipment virtually means that people can “learn by doing” without having to be physically present in a biopharmaceutical facility or needing access to equipment that may not be easily available (see example shown in Figure 1). In this way, VR offers a means of tackling one of the biggest challenges faced by those studying at university, as well as those already in employment—not to mention giving learners greater control and flexibility over how, when, and where they learn.

Handling equipment virtually means that people can “learn by doing” without having to be physically present.

There is also an important safety aspect. Learning in environments that contain hazards and that tend to be stringently controlled, such as manufacturing suites with biosafety levels (BSLs) of 2 or higher, can be difficult. VR allows training providers to create a “digital twin” model that gives safe access to these environments.

Accessibility, too, can be transformed by the use of VR. Trainers no longer need to be physically present, meaning learners—and more of them—can access experts and key opinion leaders easily and more frequently. From a language perspective there are benefits, too, where experts can provide training in a virtual environment with quick, cost-effective translation support for international audiences. Advances in natural language processing using artificial intelligence technologies means verbal translations will soon become instantaneous, further enabling the globalization of training programmes for employees and students around the world.

Perhaps most importantly, VR offers an immersive experience that can rarely be replicated in a classroom environment. Nothing can replace the skills you gain from “learning on the job” in a real facility—but being able to see the equipment, the process, and the layout in a virtual world goes a long way to bring theory to life for those starting out in their careers in bioprocessing.

Meeting the needs of patients worldwide

Digital tools inform decisions, improve bioprocesses, and enable specialized training in a way that supports and sustains biopharmaceutical industry growth, and we’re only seeing the beginning of this remarkable trend. As VR and MR in biopharma manufacturing design becomes increasingly prevalent and technologies continue to improve, medicines will make it to market faster. As an industry, we must embrace these innovative solutions. It will require focus, innovation, and investment, but it will be vital in manufacturing improvements and in providing patients worldwide with medicines they need, at a cost they can afford.

Reference

DoE to study solid dosage blends. Similar setups were later used by other companies for small-molecule solid dosage form testing.

Not only did this approach allow the first new drug applications incorporating PAT methods to be submitted to the US Food and Drug Administration (FDA), it represented a breakthrough by allowing development and quality testing to be done continuously for batch products using a multivariate approach to analyze data. Now that more companies are evaluating or using continuous processes to make solid dosage forms, applying DoE with PAT and QbD in continuous testing can eliminate the need for large and expensive pilot plants, offering considerable savings, says Ciurczak.

Use of high-throughput mini-bioreactors upstream
An analogous trend has been happening in upstream biopharmaceutical process development, as equipment has been developed to facilitate the use of PAT and DoE much earlier in the process. Within the past five years, high-throughput miniature bioreactors, which were previously used in pre-clinical screening, have been replacing bench-scale bioreactors in the scale-down exercises that are needed to scale up processes for current good manufacturing practice (cGMP) manufacturing in late-stage clinical development.

The devices eliminate the problems found with microtiter plates, spin tubes, and shake flasks, which can be difficult to automate, and allow more than 24 bioreactors to be run in parallel. They are also fitted with analytics that can take continuous readings on such crucial variables as pH, dissolved oxygen, and pressure for each of many samples.

Although developers have not yet filed new drug applications (NDAs) with FDA mentioning this technology and approach to scale-down, more companies including Genentech, Merck, Biogen, Lonza, and Fujifilm...
are working on this approach to scale-down (2). Developers are using devices such as Sartorius Stedim’s ambr 15 and 250 bioreactors (3).

**DOE software and analytics incorporated directly into micro-bioreactors**

Starting in 2015, Sartorius Stedim Stedim Biotech has integrated Umetrics’ DOE software with its ambr 15 and 250 high-throughput minibioreactors, later incorporating Nova Biomedical’s BioProfile FLEX2 automated cell culture analyzer, to simplify PAT and QbD work, and make scaleup and process optimization more efficient (4). The microbioreactors and this approach are currently being evaluated for use in gene and cell therapy development.

If anything, these developments show the durability and importance of DoE as a way to make drug development more systematic, whether for small molecules or biopharmaceuticals.

The evolution of high-throughput equipment, analytics, and DOE software promises to make these techniques, as well as QbD approaches, easier to apply to upstream biopharmaceutical development in the future.

**References**


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**Handing complexity faster: examples of DoE at work**

Design of experiments (DoE) can be used in applications ranging from pre-formulation and formulation to finished drug manufacturing, says Emil Ciurczak, spectroscopist and principal of DoraMaxx Consulting. To give an example of how DoE can enrich understanding in preformulation, consider tests that might be designed to study the interaction between an API and a single excipient, and how they affect stability. Using a univariate method, without DoE, one could take a mixture of active ingredient and excipient and put it through different stability studies (i.e., exposing it to heat, cold, light, and other variables) and hold it for 4–20 weeks and look for the breakdown point. This would provide information on interactions between the API and excipient, Ciurczak explains, but only one combination could be tested at a time. The time required for testing would be significant, after which high-performance liquid chromatography (HPLC) and thin layer chromatography (TLC) testing would still be required.

Using DoE, one could choose to consider the API, plus seven of the excipients that are most often used with that active, and test for eight different parameters, says Ciurczak. This would mean 8 times 7 mixtures, which would be put in vials in racks. Near Infrared (NIR) or Raman spectroscopy could then be used to test samples every day and plot any changes. The vials would be tested with chromatography. Not only would this approach be much faster, it would be much more exact, and show clearly when each different combination of API and excipient reacted. In drug synthesis, where the highest yield is the goal, DoE could be used to select the most stable alternative with the highest yield. In formulation, it can help determine the best formulation based on stability and release pattern, Ciurczak explains.

**QbD and the Design Space**

In pharmaceutical quality by design (QbD), DoE is used to define the design space for a product, correlating critical quality attributes and process parameters, allowing quality to be optimized by staying within specific boundaries. For these tests, one would need to know the process parameters and to test a wide range of combinations of API with various excipients and ingredients, using a full-sized batch for testing. As Ciurczak explains, the Plackett Burman approach (1) would often be used for the first phase of testing. Optimum levels would be set for each parameter, with a deviation of plus or minus 10% and Partial Least Squares regression would be used to show whether deviation is positive or negative. A second testing stage would determine the upper and lower limits of the design space, allowing formulators to tweak formulations to ensure that variations in ingredients would not affect product quality. Results could be used to optimize other parameters (e.g., shelf life).

**Reference**


— Agnes Shanley
Meeting E&L Expectations

As regulatory bodies extend the oversight of E&L testing, companies working with drug products need to make provisions on how to best comply with the evolving expectations.

Felicity Thomas

Extractables and leachables (E&L) testing, to a certain degree, is a requirement for nearly all drug product submissions to the relevant regulatory bodies, unsurprising given the fact that patient safety is of paramount importance. Guidance documents provided by regulators, however, do not detail how E&L evaluations should be performed by companies, and expectations by regulators have become more stringent in recent years.

“Nearly all drug products submissions require at least some level of E&L evaluation, with the possible exception for lower-risk items, such as oral solid dosage forms,” says Derek Wood, associate director, PPD Laboratories. “Failure to comply with regulatory expectations regarding E&L evaluation can result in drug product approval delays.”

Importance of E&L testing

Used to determine whether unwanted, and potentially harmful, compounds can migrate into a drug product from packaging, delivery system, or manufacturing surface, under normal or extreme circumstances, E&L testing is of critical importance in drug development, confirms Andrew Kolbert, president and chief technology officer at Avomeen. “E&L testing results must be included with FDA [US Food and Drug Administration] drug submissions, for example,” he states.

“The main driver of all regulatory authority in drug registration, such as product approval and drug/device combination approvals, is patient safety. Product efficacy also provides a basis for regulatory involvement,” notes Frank Hoffmann-Geim, director regulatory affairs at Schott Pharmaceutical Systems. “One critical parameter of patient safety, as well as for avoidance of loss of efficacy, is to avoid any kind of negative interaction between the inner surface of the drug container and the medicine inside.”

Ultimately, compounds that have extracted or leached into the drug product can not only result in direct toxicity to the patient but can also impact the efficacy of the drug product, which has the potential to also impede patient safety, emphasizes Wood. “To ensure controls for protecting patient safety, E&L evaluation is a key requirement for most regulatory filings and is critical for consideration of drug product safety, efficacy, and quality,” he adds.

However, even to this day, Wood explains that there are many instances where insufficient or incomplete E&L testing is occurring and, as a result, causing delays or even complete rejections of regulatory submissions. In illustration of his point, Wood raises an example from the late 1990s, involving a leachable vulcanizing agent in an Eprex anaemia drug product. The leachable agent was found to cause an increase in cases of pure red-cell aplasia (PRCA) in some patients, which resulted in the product being recalled from 17 countries (1).

“The source of the problem in the Eprex anaemia example was determined to be due to a change in the formulation that was made wherein the original biologically derived solubilizing agent, human serum albumin, was replaced by polysorbate 80,” Wood says. “Along with the formulation change, the manufacturer changed the rubber material of the syringe from a coated plunger to that of an uncoated plunger. These modifications enabled an interaction between the rubber plunger and the polysorbate 80 in the new formulation, resulting in a vulcanization agent (2) within the rubber to leach into the drug product.”

Giving a further example, Wood highlights the cases in 2010 and 2011, where multiple lots of Lipitor, Glumetza, and Tylenol were recalled when patients noticed a musty odour coming from opened drug product bottle containers (3). “It was found that the musty odour was from 2,4,6-tribromoanisole.
(2,4,6-TBA), a byproduct of a chemical preservative used for the wooden shipping pallets on which the products were stored and shipped,” he reveals. “The preservative byproduct (2,4,6-TBA) leached out from the wooden pallets and migrated into the drug products’ containers.”

Size matters: Potential concerns with biologics

It is widely known that increasing numbers of large-molecule drugs are entering the development pipeline and being presented to regulatory bodies for review. However, these complex molecules present a variety of potential concerns relating to E&L testing.

“Although it is best practice to perform leachable testing as part of your registration stability for all drugs, it is especially more important to do this for biologics,” emphasizes Kolbert. “This is because in addition to leachable toxicity, large-molecule drug substances pose greater risks of interacting with the packaging, delivery system, or manufacturing surface in ways that can compromise drug activity.”

Biopharmaceutical products are generally developed as parenteral formulations, which is an administration route considered to be higher risk for E&L by regulatory bodies. “Although many small molecules are parenterally administered as well, the uniqueness of large-molecule drugs is they more often include certain excipients that are present to enhance the stability or solubility of the active ingredient,” explains Wood. For example, surfactants such as polysorbates and poloxamers, which are used to help prevent protein aggregation or degradation and aid with solubilization or emulsification, can enhance the migration of leachables, he adds.

Additionally, biopharmaceuticals present challenges due to the number of active sites present within the molecules themselves that have the capacity to react with leachables, Wood iterates. “The activity-dependent, tertiary structure of biopharmaceutical products can be negatively impacted by leachables, such as silicone oil,” he says. “Biopharmaceutical products can be denatured by exposure to inorganic leachables such as certain metals.”

Another important consideration for Wood is drug product manufacturing. “Biologic drugs typically are manufactured using a single-use system, in which disposable plastics and bags are utilized instead of traditional stainless-steel vessels,” he asserts. “The disposable manufacturing components have a higher propensity to leach compared to the stainless-steel components.”

Companies may also be cautious in terms of the amount of materials available for E&L evaluations. For many cell-based production techniques, small amounts of product are manufactured with a high cost-per-unit volume, which means that a laboratory must approach E&L testing with an appropriate study design so that the sensitivity required can be attained at a scaled-down volume compared with traditional small-molecule products, Wood stressed.

Lyophilization may also be an attributing factor to consider for E&L testing, as many biologics are lyophilized to improve shelf-life storage stability. “Although perhaps counter-intuitive to the typical expectation that liquid solvents would promote more leaching than dry powder, our research (4,5) has revealed that in the case of lyophilized products stored in a vial with rubber septum, there can be a greater propensity for volatile and semi-volatile leachable compounds migration into the lyophilized cake than there would be for the product in liquid form,” Wood says.

Furthermore, packaging and packaging systems are being affected by the increasing demands of biological products, and consequently are becoming more complex. “Of particular importance is the use of different materials for components of such packaging,” confirms Hoffmann-Geim.

“Much of the United States Pharmacopeia (USP) regulations and norms concerning E&L testing arose from the use of glass vials, because they were the most common container for injectable drugs,” he continues. “Over the years, primary packaging manufacturers have introduced syringes made of glass as well as of polymer, both comprising rubber components as stoppers, tipcaps, or plungers. Now, the norms are evolving so that pharmaceutical companies have to not only consider the packaging itself, like the glass barrel of a syringe, but also the additional components made of different materials and which will come into contact with the drugs.”

Regulatory requirements and best practices

Multiple guidance documents have been published by FDA and the European Medicines Agency (EMA) to support industry with the legal requirements of ensuring that impurities in drug substances and drug products, above a certain threshold, are monitored and/or characterized. However, the guidance is generally not prescriptive and can be open to interpretation in terms of implementation, stresses Kolbert.

Highlighting experiences with FDA specifically, Kolbert continues to explain that as a result of the non-prescriptive nature of the guidance, it is possible for E&L testing expectations to change readily without regulations changing. “Over time, FDA has increased the scope of products for which it expects E&L testing results,” he says. “The agency used to be concerned only with the most high-risk products. FDA has now moved on to also focus on products that are low risk—such as oral capsules and tablets.”
Additionally, Kolbert reveals that FDA has expanded its oversight of E&L testing to include components that are not necessarily associated with risk factors, such as manufacturing components involved in the drug production process. “So, if a drug product has to pass through a gasket or hose for any amount of time, FDA expects E&L testing to be performed on those components,” he adds.

“Due to the lack of detail and clear direction in the evaluation of E&L, various industry group guidance documents also have been established over the years to help complement the regulatory guidance with best practice ‘how-to’ approaches for conducting E&L studies and reporting thresholds,” Wood notes. A main industry group whose approaches to E&L testing have been adopted by regulatory bodies globally is the Product Quality Research Institute (PQRI) [6].

“One of the more recent developments over the past few years is the ongoing establishment in the USP of more extensive E&L general chapters and related monographs that are aligned with PQRI and regulatory documents, regarding the approach and reporting of leachables,” Wood says. “This has helped to add consistency to the approach for these types of studies, bringing together the accepted industry group and regulatory guidance.”

Testing is typically outsourced
Pharma and drug-device companies have a tendency to outsource E&L testing to laboratories that have extensive experience with a wide range of systems and materials for a variety of administration routes, Wood reveals. “A contract E&L laboratory should be able to provide effective consultation for proper study design to help navigate regulatory expectations,” he says.

In agreement, Kolbert adds that for the majority of pharma companies the expertise required for E&L testing of materials, such as plastic, polymer, and rubber, are not typically core competencies. To address the evolving E&L testing expectations of regulatory bodies, he specifies that contract research organizations (CROs) should be employing experts from the metals, plastics, and polymer industries.

“It is often difficult for pharma companies to keep up with changing E&L guidance because regulatory bodies can take issue with the E&L testing methods used without precedent,” Kolbert explains.

Greater time and effort is required by companies and outsourced partners to learn and understand how to meet regulatory expectations.

“Usually a CRO finds out about these things because one company receives a finding and word gets around the industry through the CRO. When a company submits a product for review, then learns there is a regulatory requirement to consider additional factors, it can cost the company a great deal of additional time and money. Often, the entity must ask the CRO to do the work in a compressed timeframe. Such rush requests can be quite costly.”

Growing importance
In light of the evolving regulatory stance on E&L testing, greater time and effort is required by companies and outsourced partners to learn and understand how to meet regulatory expectations. “The best way for CROs, in particular, to prepare for more stringent standards in E&L testing that may come in the future is to hire experts from a wide variety of industries to provide a greater scope of expertise,” Kolbert says.

“For companies with large drug product pipelines especially, there are benefits to arriving at a list of platform material components to be used to save time and cost on performing separate extractables studies later,” adds Wood. “We have seen this with multiple large pharmaceutical companies, where they establish a material platform for container/closure or device components, such as vial stoppers used for storing liquid injectable products. All the potential stoppers to be used for all their products are collected and a large controlled extraction study is performed, and then that data can be leveraged for many products in the future, saving time and cost. Leachable studies are still required, but the extractables piece is already in place. The component extractables data can be leveraged for use on new products, thereby helping to shorten the overall E&L timeline.”

From the primary packaging manufacturer perspective, Hoffmann-Geim highlights the potential challenges of biologics, which are very sensitive to chemical interactions with other materials. “The importance of E&L assessments is going to grow in coming years,” he summarizes. “It’s of increasing importance that providers of primary packaging work closely with pharma companies to understand which ingredients and molecules are being used in our containers. It’s not enough to only sell a piece of glass or a piece of polymer. Primary packaging must also be tailored directly to a specific drug, the needs of the patients, and the therapy to ensure patient safety.”

References
Applying Lessons Learned from the Semiconductor Industry

Characterization of raw materials and supply-chain control allow more rigorous control of the manufacturing process.

Claudia Berrón is senior vice-president, Strategy and Commercial Operations, Biopharma Production, and Gary Dailey is vice-president, Global Marketing, Electronic Materials, both at Avantor.

Two of the world’s most complex manufacturing industries—semiconductor fabrication and biopharmaceutical production—share a common fundamental objective: to maximize process yields through rigorous control of production equipment and process variables.

One process variable that the semiconductor industry has long focused on is raw material quality. Thorough analysis and full characterization of each raw material used will determine the precise composition, down to the parts-per-trillion level, providing information on how this composition might impact the production process. Recently, biopharmaceutical manufacturers have also begun to focus on understanding and controlling the characteristics of the materials they use. In upstream and downstream processes, biopharma manufacturers seek to correlate raw material data with variations in their bioreactor and process chromatography yields, with a goal of achieving greater predictability and control of process results. In formulation, a lot of emphasis goes into correlating how variables in excipients affect drug product stability (and therefore bioavailability) throughout the shelf life of the product.

There is significant value in assessing and potentially applying the semiconductor industry’s highly developed advanced materials analysis, characterization, and supply-chain control practices to materials’ management and process control issues in biopharmaceutical operations.

Maximizing semiconductor yields

Semiconductor manufacturing is expensive. The cost of building a semiconductor foundry can exceed US$10 billion (more than €9 billion) when all the tooling, automation and management systems, environmental controls, and quality control costs are considered (1). And once in place, the additional cost of the raw materials and associated processing to make a single wafer adds to this expense, which is why semiconductor manufacturing operations must focus on maximizing process yields.

At the beginning of the process, a raw wafer, composed of a highly refined form of silicon, can cost approximately US$500 (€450) (1). There can be 25 to 50 wafers in a batch, and a large fabrication plant can process 50,000 wafers per month, with each wafer going through more than 1000 process steps. A wafer containing finished memory chips can be valued in excess of US$1600 (€1450), and a finished high-end processor wafer can reach US$5000 (€4540) (1). Every process step has an impact on yield and, ultimately, profitability.

It is crucial for a manufacturer to control process variables and eliminate unknown factors that could interfere with or contaminate each step of the process. In complex integrated circuits such as processors in smart phones, a single chip can contain several billion transistors, each only a few nanometers wide. If any foreign material is present in those transistors, the chip may not function according to its design. The risks associated with these challenges has led the semiconductor industry and the companies that supply its materials to make investments in ultra-precise materials characterization procedures in order to maximize predictability of manufacturing outcomes.

Each process step is controlled by a process of record that defines every detail. For example, the exact chemical makeup and level of impurities in a chemistry used to remove post-etch residue must be characterized down to the parts-per-trillion level. While it may not be practical to manufacture a chemical to meet 100% purity, the chemical should be as pure as the best technology can deliver. Any trace materials in the post-etch strippers used in the process need to be identified and quantified so they may be incorporated into a process of record and monitored.
Once set, the foundry operator has the statistical data to assume that, with the properly characterized material, that post-etch residue step will yield the defined result, and the wafer can move on to the next process step. Any variation in trace elements—even just a few parts per billion—can result in less-than-desired post-etch cleaning that may interrupt production and lead to significant costs in time, labour, testing, materials, and other areas to investigate the cause of variation.

**Improving biopharma stability and yield**

Materials characterization has also been of interest in the biopharmaceutical industry; however, rather than yield, manufacturers were initially interested in using it to determine stability. Highly accurate and detailed materials characterization has been performed for the excipients used in fill/finish processing. During this process, the biological drug substance is combined with a variety of excipients to enable delivery and stability and is formulated into a final drug product. Because the excipients would be used within the body during the administration of the final drug, such characterization is necessary, and requirements have increased over time to satisfy strict regulatory and safety requirements. Also critical is the stability of the drug product; reducing drug product degradation during storage has become a significant focus for raw material characterization.

From this initial focus on meeting regulatory requirements and drug product stability, biopharma producers seeking to improve their process yields have more recently begun to assess the impact of stricter and more comprehensive materials characterization in upstream and downstream process steps.

Unlike fabrication of precisely engineered semiconductors, however, biologics production has an inherent variability. Even under similar process conditions, a molecule can react slightly but measurably differently, often depending on genetic sequencing for that particular molecule. All these molecules react differently to a variety of trace metals. When large-scale production of biologic drugs originally began, the focus was on characterizing excipients, but not nearly as much attention was paid to the buffers, salts, cell culture media, and other materials used upstream, until further study and analysis tied to improved process control was undertaken.

**Unlike fabrication of precisely engineered semiconductors, however, biologics production has an inherent variability.**

A further challenge to understanding and applying rigorous materials characterization practices to biologics production is that the presence of trace minerals can actually be beneficial to upstream and downstream processes. The addition of metals, including iron, manganese, and zinc, can enhance glycosylation yields upstream in certain molecules. It has also been shown that understanding and controlling the ratio of trace metals, as well as their levels, can impact upstream yields positively or negatively—all dependent on the molecule.

As biopharmaceutical manufacturers have begun turning their attention to improving trace material characterization, they have determined the critical importance of lot-to-lot consistency of the trace elements in critical materials used upstream and downstream. Variation to that consistency, including minimal changes at the parts-per-billion levels, can impact glycosylation patterns in the reactor, reduce overall target cell growth upstream, and impact recovery downstream. This knowledge has been gained by the biopharma industry while responding to problems or unexpected shortfalls in upstream yields. As a result of lessons learned, the biopharma industry is turning to a more formal and comprehensive process of trace materials characterization as a tool to boost yields.

**Applying best practices**

The biopharma industry has already made great strides in improving its trace materials characterization efforts and applying that data to improving upstream and downstream yields. To advance this further, three rigorous processes used in the semiconductor industry can be applied to the biopharma industry: statistical control, analytical capabilities, and in-depth management and control of global supply-chain resources.

**Statistical control.** It is well established in the semiconductor industry that every process step, including a change to a step, goes through a comprehensive qualification process that ensures every material used in a process is qualified at specific ranges down to parts-per-trillion levels. Once qualified, suppliers commit to and document that every lot has the same level of trace materials. Some suppliers are able to commit to characterizing, within two sigma, each of the components of a certificate of analysis (CoA). In fact, the trend is moving in the direction of even stricter, three sigma levels of control of impurities in raw materials.

Although biopharma processes can deliver projected yields with a parts-per-billion characterization, there are advantages to adopting the comprehensive model used by the semiconductor industry. By establishing the principle that all materials used in upstream and downstream processes will be fully characterized and controlled, it should become easier to predict process yields, identify whether materials are contributing to a shortfall, and leverage the ability to modify the levels and ratios of trace metals in bioreactors to potentially improve yields.
Analytical capabilities. For biopharma manufacturers to effectively implement statistical control along the same lines as the semiconductor industry, they will need to increase investments in analytical capabilities and tools and begin to implement a data-driven production environment. Compared to other process industries, the biopharmaceutical industry lags in the aggressive use of data and predictive analytics to uncover ways to improve productivity, yields, and costs. The industry is, however, making significant investments to improve its use of data.

The objective is to use production data to optimize the process, then manage the critical parameters within it so it can be reliably repeated. These efforts are being conducted for both upstream and downstream production, but often in isolation. There is an opportunity to expand the application of data analytics beyond a specific process component to more completely characterize the entire process, including the raw materials used in both upstream and downstream production. Ultimately, this can be integrated into the overall optimization efforts for the entire production process.

Supply-chain control. One of the most important benefits of greater statistical control and analytical capabilities will be the ability of biopharma manufacturers to have more complete control of the quality of the materials they receive from their global supply chains. This is a key capability that has been established by the semiconductor industry to prevent variations in trace materials from impacting their operations.

For example, there are multiple processes in semiconductor fabrication that use organic solvents. Many of the precursors for these solvents are manufactured by petrochemical producers, who normally don’t need to exercise ultra-stringent control of impurities. As a result, suppliers of solvents to the semiconductor industry have invested in the tools and processes to manufacture their products with tight purity levels and fully characterized CoAs. In addition, they work with their suppliers to document any changes made to source materials or production processes, well ahead of time. This lead time lets the supplier build stock and evaluate that change as it comes through the process to see if it introduces change to their end product.

This same attention to detail and supply-chain control is also crucial for biopharma materials for essentially the same reason; minor changes in processes or raw materials used upstream can significantly affect the downstream product.

One of the most important benefits of greater statistical control and analytical capabilities will be more complete control of the quality of materials [manufacturers] receive from their global supply chains.

In addition to variation caused by trace minerals, biopharma processes may use organic or plant-based materials. For example, sucrose and galactose are sugars derived from sugar beets. Plant-based materials will inevitably have some variation in their properties. There are significant advantages to working with suppliers who have implemented technologies and purification to further purify and narrow variability in elemental impurities that would affect biopharmaceutical production.

By building networks of suppliers who are fully committed to following global current good manufacturing practices for manufacturing processes and documenting all source materials completely, it is possible for the biopharma industry to achieve a similar level of materials management and control over the variability and quality of critical sourced components.

Cross-collaboration

Although the two industries have vast differences, both semiconductor manufacturers and biopharmaceutical manufacturers have some core common ground. Both begin with raw materials and process those materials in a highly controlled, multi-step fashion to produce products of high value. And both industries are driven to invest time and resources into continuously improving those processes to achieve better yields and return on investment.

By applying some of the hard-earned principles and approaches the semiconductor industry has developed, the biopharmaceutical industry has the potential to significantly advance its ability to analyze, characterize, and control the trace elemental properties of the materials used in biologics production and ultimately achieve new milestones in process efficiency and yields.

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Company Description
Catalent is the leading global provider of advanced delivery technologies, development, and manufacturing solutions for drugs, biologics, gene therapies, and consumer health products. With over 85 years serving the industry, Catalent has the proven expertise, superior technologies, and flexible solutions at the right scale to help ensure successful product development, launch, tech transfer, and reliable global supply.

Catalent has built this expertise through helping partners of all sizes, from the smallest innovators to the largest of biopharmaceutical leaders, to advance thousands of molecules through each phase of development and on to commercial supply. By arranging our expertise, capabilities, technologies, and capacity, we provide services from specific, tailored programme support or comprehensive, integrated solutions that are fast, flexible, reliable, and that help our partners reduce project risk. In fact, our team of nearly 13,000 at 35 sites develop more than 700 projects and help launch in excess of 200 products every year. We produce more than 72 billion doses of over 7000 products for more than 1000 customers—or 1 in 20 doses taken by patients globally. Our passion is to help unlock the full potential of your product.

More products better treatments reliably supplied™

Technology Highlights
With our wide range of expert services—including analytical, biologics, preformulation, and formulation—we drive faster, more efficient development timelines and produce better products. These include:

• Paragon Gene Therapy, part of Catalent Biologics, focuses on transformative technologies, including adeno-associated virus (AAV) gene therapies, next-generation vaccines, and oncology immunotherapies.

• GPeX® Boost technology for advanced cell expression, and advanced biopharmaceutical development, analytical and manufacturing.

• SMARTag® technology for antibody-drug conjugation, affording precision design of next-generation biologic therapies.

• OneBio™ Suite, a single solution from cell line development through clinical supply reduces timelines, risk, and complexity.

• OptiForm® Solution Suite to assist in rapid, optimized dose form development.

• Bioavailability enhancement including lipid-based systems, Pharmatek SD™ spray dry technology, particle-size engineering, and OptiMelt® hot melt extrusion.

• Unique delivery technologies: including OptiShell® gelatin-free capsule technology, the Zydus® orally disintegrating tablet platform, and controlled release dose design, as well as inhaled and injectable dose forms.

• Catalent R.P. Scherer Softgel is a global leader in innovative oral and topical softgel technologies, and nearly 90% of NCEs approved by the FDA over the last 25 years have been developed by us.

Contact details
Catalent
14 Schoolhouse Road,
Somerset, NJ 08873, USA
Tel.+1 888 765 8846 (USA)
or 00800 88 55 6178 (EU/ROW)
www.catalent.com
solutions@catalent.com
**Company Description**

Lonza Pharma & Biotech is the leader in capsule-based solutions and services, proudly offering Capsugel® products. With an invaluable global production and supply chain footprint, we strive to provide the highest level of quality products and offer regulatory expertise to our 2000 pharmaceutical customers worldwide.

For more than 100 years, biopharmaceutical companies have relied on the quality, consistency and functional innovations Capsugel® has delivered. Today, we produce more than 200 billion capsules for over 100 countries.

**Markets Served**

Capsugel® creates, develops, and manufactures a wide range of innovative dosage forms for the biopharmaceutical and consumer health & nutrition industries.

**Major Products/Services**

With a diverse portfolio including HPMC, dry-powder inhalation capsules, and specialized clinical capsules, we are a global leader in capsule development and manufacturing, bringing unmatched products and technical support to our worldwide customer base.

- **Immediate release**: Coni-Snap® Gelatin, Vcaps® Plus, Vcaps® Gen C, Plantcaps®
- **Modified release**: Vcaps® Enteric, DRcaps™
- **Dry-Powder Inhalation**: Zephyr™ portfolio
- **R&D–Clinical**: PCcaps®, DBcaps®, Colorista®
- **Patient-centric–End to end**: Coni-Snap® Sprinkle, Press-Fit®, Licaps®

The Lonza Engine™ portfolio includes equipment for micronization, capsule filling, and sealing and powder microdosing. It supports bioavailability enhancement, encapsulation and early-phase clinical development technologies.

**Facilities**

Meeting the needs of customers in over 100 countries requires a reliable and highly efficient integrated global network of manufacturing sites. With our global scale, we have established a rigorous programme to certify our vendors and their products that provides a best practice for the industry.

**Contact details**

Capsugel® | Lonza Pharma & Biotech
Rijksweg 11, B-2880 Bornem, Belgium
Tel. +33 389 205 725
Fax. +33 (0) 3-89-41-48-11
www.capsugel.com/market-segments/biopharmaceuticals
solutions.emea@lonza.com
Shimadzu Europa GmbH

Company Description
Shimadzu is one of the worldwide leading manufacturers of analytical instrumentation, and for over 50 years, the European headquarters has been located in Duisburg, Germany. The company's equipment and systems are used as essential tools for research, development, and quality control of consumer goods in all areas of pharmaceutical and environmental industries, food safety testing, consumer protection, and healthcare to contribute to society through science and technology. Chromatography, mass spectrometry, spectroscopy, life sciences, and material testing make up a homogeneous yet versatile offering. Along with many "industry first" technologies and products Shimadzu has created and invented since 1875, there has also been the exceptional achievement of the 2002 Nobel Prize for Chemistry to Shimadzu engineer Koichi Tanaka for his outstanding contributions in the field of mass spectrometry. Shimadzu is focused on top quality when developing products, including ease of operation and optimum service. The company manufactures according to internationally renowned quality standards, including Pharmacopeia, ISO, FDA, GLP, and GMP.

Markets Served
Shimadzu's analyzers and equipment are applied in the food industry, clinical and pharmaceutical field, automotive industry, chemical, petrochemical, life sciences and biotech, cosmetics, semiconductor and nutrition industries, as well as in the flavors and fragrances business. Research institutes, privately-run laboratories, administrations and universities complete the list of clients. The systems are used in routine and high-end applications, process and quality control, as well as R&D.

Major Products/Services
Nexera LC-40 series—Experience New Benchmarks
Shimadzu's Nexera series of UHPLC systems offers groundbreaking technology in terms of intelligence, efficiency and design. Advanced AI capabilities and lab management using the Internet of Things (IoT) have been integrated to monitor performance and resource allocation. They make the Nexera systems a leading-edge and user-friendly solution for versatile industries, setting new benchmarks in UHPLC.

The Nexera series of UHPLC systems offers groundbreaking technology in terms of intelligence, efficiency and design.

LCMS-9030 Q-TOF—Greater accuracy with higher sensitivity
The LCMS-9030 quadrupole time-of-flight liquid chromatograph mass spectrometer of Shimadzu is a research grade mass spectrometer designed to deliver high-resolution, accurate-mass detection with incredibly fast data acquisition rates, allowing scientists to identify and quantify more compounds with greater confidence. It provides a new solution for analyzing even the most complex samples and integrates the world's fastest and most sensitive quadrupole technology with TOF architecture.

The LCMS-9030 Q-TOF system provides greater accuracy with higher sensitivity

Facilities
Shimadzu operates production facilities and distribution centres in 74 countries. In the European headquarters in Germany, the Laboratory World provides testing and training facilities for customers from all over Europe. With over 1500 m² floor space, Shimadzu's entire product range is available—from chromatographs, spectrophotometers, TOC analyzers, mass spectrometers, and balances to material testing machines. In Europe, Shimadzu runs subsidiaries and branches in Austria, Albania, Belgium, Bosnia, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, France, Germany, Hungary, Italy, Luxemburg, Macedonia, Montenegro, Moscow, The Netherlands, Russia, Romania, Serbia, Slovakia, Switzerland, and the United Kingdom.

Contact details
Shimadzu Europa GmbH
Albert-Hahn-Str. 6-10
47269 Duisburg, Germany
Tel. +49-203-76 87 0
Fax. +49-203-76 66 25
www.shimadzu.eu
shimadzu@shimadzu.eu
Veltek Associates, Inc.

Company Description
Veltek Associates, Inc. (VAI), with over 35 years of experience, has developed an extensive line of products and services that offer solutions to the challenges of contamination control within aseptic manufacturing and controlled environments. With over 135 patents, we are committed to continual innovation and improvement in our products to satisfy current and future regulatory requirements.

Markets Served
• Pharmaceutical
• Biotechnology
• Medical Device
• Laboratory Research
• Healthcare/Hospitals
• Compounding Pharmacies

Major Products/Services
VAI’s innovative products include:
• **Chemicals**—VAI offers a complete line of sterile and non-sterile chemicals. With EPA-registered disinfectants and sporicides and cleaners including buffers, water, residue removers, and lubricants, operations are able to maintain critical environments while staying compliant.

• **Dry and Saturated Wipes**—VAI’s wipers offer excellent particulate performance and are for use in all cleanroom settings. A variety of VAI’s sterile chemicals are available in saturated wipers including sterile sodium hypochlorite and hydrogen peroxide wipes.

• **Process Cleaners**—VAI offers a complete line of clean-in-place detergents for manual, soak, or spray applications. Our process cleaners remove a wide array of organic or inorganic soils.

• **Cleanroom Documentation**—VAI’s line of cleanroom documentation offers a synthetic writing substrate with extremely low particulation, customizable documentation, and a HEPA filtered printer to print directly in controlled environments.

• **RFID Tracking**—VAI’s Core2Scan system is an identification and tracking system that pairs RFID asset and procedural identification devices, readers, and software tracking technology with a facility’s equipment, products, and/or procedures.

• **Garments**—VAI has launched a redesigned line of sterile disposable garments that include low particulation, high breathability, and comfort while maintaining an athletic design and personal protection.

• **Cart Transfer Systems**—VAI’s Cart2Core® simplifies correct aseptic cart transference by allowing the cart top to detach from the base. With one lift of the handle and a slide, any cart top is transferred from one cart base to another, leaving the potential contamination behind.

• **Environmental Monitoring**—VAI’s viable monitoring equipment has been an industry standard for over 30 years by helping operations monitor, capture, and evaluate the ingress of viable contamination. In addition to viable monitoring, VAI offers a complete line of particle counters.

• **Cleaning Equipment**—VAI offers a completely sterilizable, all in one, spray, mop, and fog cleaning system. The Core2Clean is an innovative way to ensure cleaning and disinfection within the cleanroom is being done correctly and efficiently.

VAI’s technical services include:
• Consulting Services
• Cleaning and Disinfection Systems Evaluation
• Disinfectant Validation Studies
• Anti-Microbial Effectiveness Testing
• Personnel Gowning Training
• Aseptic Processing Systems
• Viable Air Monitoring Evaluation

Facilities
VAI is headquartered in Malvern, PA USA with satellite sales offices located worldwide. VAI in addition, is able to serve the pharmaceutical and biotechnology industries in an even greater capacity through our 120 distribution partners.

Contact details
Veltek Associates, Inc.
15 Lee Blvd. Malvern, PA 19355
Tel. +1-610-644-8335
Fax. +1-610-644-8336
vai@sterile.com
www.sterile.com
Investigating Combination Product Failures

Q: We have recently contracted with a client to manufacture a pre-filled syringe. Can you tell me what changes I should make to my investigation procedure when investigating deviations and complaints for this type of combination product?

A: The purpose of performing an investigation into a deviation is to determine why the deviation happened and what impact it has on the product quality. It is important to determine the ‘root cause’ of the deviation. The process used in industry to determine the root cause is the investigation procedure. The investigator should review various quality and manufacturing systems to determine whether they were the cause of the deviation under investigation. Each investigation must address the following elements: root cause, impact to the material or product, the immediate correction taken, the corrective action to prevent re-occurrence for specific product/operation, and the preventive action taken to prevent re-occurrence for all products/operations. The complication with combination products is that the investigation procedure needs to accommodate both the drug and device components of the product.

One size does not fit all. Simple errors require simple corrections, while serious deviations require broader investigations. The complexity of the investigation is related not only to the seriousness of the investigation but also to the complexity of the factors that could influence the outcome. The best trait to have as an investigator is inquisitiveness. Continuing to ask questions and avoiding assumptions leads to better outcomes. Using other tools, such as fishbone diagrams and determination of most probable number (MPN), are to be encouraged, but they do not take the place of asking questions. The best way to ensure events are not related is to try and relate them, not the other way around. Keep in mind that human error is rarely a true root cause. In addition, you should always verify the facts of the investigation.

Once you develop an investigational history with the pre-filled syringe, include a historical review in your investigation. This review should determine if the deviation occurred with this or other products, with the specific manufacturing line or other manufacturing lines, and/or with one group of operators or multiple sets of operators. The historical review can help you prioritize the resources and aid in your detailed system review.

In the situation you described, you can provide a historical review for the drug component part of the pre-filled syringe but you will need to outreach to the syringe supplier and your client to start developing the historical review for the device component until you have a body of knowledge for this component. The best way to obtain necessary information for the investigation of the device component is to establish a communication channel between your company and the supplier of the syringe, with your client’s knowledge and approval. It would be wise to codify what information you would like to have access to through quality agreements with both the syringe supplier and your client.

The detailed investigation should include a review of equipment and machinery, the manufacturing process, the raw materials used in manufacturing, the specifications, the environment, and finally, the operators. These systems are not the only areas you should look at but are the most probable areas where you will uncover the root cause of the deviation. The raw material or supplier system may need to be updated to accommodate the syringe supplier. Rather than rely on the client’s evaluation and audit of the syringe supplier, it would be beneficial for your company to perform their own audit and assessment and establish a quality agreement. Inform your client that you want to develop your relationship with the syringe supplier to assure their assistance and timely responses for an investigation; make sure you inform your client when you do reach out to the supplier during an investigation. This will help facilitate both your client’s and the syringe supplier’s involvement and open the lines of communication should you require either of their assistance for an investigation.

Results from the investigation must be documented. The written narrative should clearly explain what happened, when it happened, and who was involved or observed what happened. The narrative documents the solution and rationale for the root cause that was determined through the investigation process. This should also include any action being taken by the syringe supplier to assure their assistance and timely responses for an investigation; make sure you inform your client when you do reach out to the supplier during an investigation. This will help facilitate both your client’s and the syringe supplier’s involvement and open the lines of communication should you require either of their assistance for an investigation.

The key to any successful investigation is not stopping too soon, and assuming you have the solution prior to completing the investigation. If you follow your investigation procedure, make adjustments to accommodate the new component, and thoroughly document your results, you should have an acceptable investigation regardless of whether you are manufacturing a traditional product or a combination product.
With 3 NEW facilities, Catalent has expanded its European solutions and expertise by adding two sites in the U.K. focused on oral drug development and spray dry technology, and one in Italy* providing clinical and commercial manufacturing, fill finish and packaging for tech transfers and new launches of oral dose and biologics. These new sites complement 11 existing Catalent manufacturing facilities that provide clinical logistics and supply, softgel and oral technologies, and drug product manufacturing of injectables, with the flexibility to offer individual services and integrated solutions. The leading European development, delivery and supply network.

*Subject to transaction closing