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Was it natural zoonotic spillover that catapulted SARS-CoV-2 from an emerging virus into a pandemic pathogen or was it something much more sinister? Is it at all possible that a lab leak in Wuhan, China, was the spark that lit the fuse? Debate and discussion about the origin of the virus that causes COVID-19 have been at the forefront of the global consciousness since the first cases were reported in December 2019.

Early on, whispers of a potentially engineered virus quickly grew to a roar and fuelled speculation that China was behind the pandemic. This narrative was so pervasive that, in February 2020, a group of 27 public health scientists published a letter in The Lancet disputing the lab leak theory and announcing their support of their counterparts in China: the scientists, public health officials, and medical professionals combatting the pandemic (1).

"The rapid, open, and transparent sharing of data on this outbreak is now being threatened by rumours and misinformation around its origins," wrote the authors, who all declared no competing interests in their disclosures as recommended by the International Committee of Medical Journal Editors. "We stand together to strongly condemn conspiracy theories suggesting that COVID-19 does not have a natural origin."

And although it’s true that analyses of the genomic sequence of the virus subsequently pointed to natural origins, the questions regarding China’s role persisted, led by pesky discrepancies and conflicting reports.

Fast forward to June 2021 and new evidence that has breathed new life into those origin questions. In an update to the February 2020 letter, The Lancet has published an addendum with revised disclosure statements from virologist and investigator Peter Daszak, one of the 27 authors (2). In the revised document, Daszak noted that his remuneration is paid solely in the form of a salary from EcoHealth Alliance, a New York-based nonprofit research foundation of which he is president. The company has reportedly worked directly with Wuhan laboratories and funded gain-of-function research at China’s Wuhan Institute of Virology.

Consider, too, other odd associations. Recent reports have uncovered financial ties between Google and EcoHealth Alliance. This comes after accusations that the tech giant was censoring lab leak “conspiracy theory” stories in its search results. Google’s health lead, David Feinberg, has dismissed those reports, insisting that the company is simply taking steps to protect users from unverified information.

Are these coincidences or “where there’s smoke, there’s fire” situations? It’s unclear. But they add to the bank of troublesome questions standing in the way of the truth about COVID-19.

The questions extend beyond origin theory, though. With US Food and Drug Administration’s green lighting of vaccines for adolescents and young adults comes hesitation over long-term effects: What is the effect on fertility? Do the vaccines cause heart inflammation? Robert Malone, an mRNA researcher, appeared on television recently, expressing strong concern over the risk-benefit analysis of vaccination for young adults (3), and the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices recently met to discuss instances of myocarditis or pericarditis in people aged 30 and younger who have received an mRNA COVID-19 vaccine.

Of course, the answer to our ultimate question is that we may never know.

We may never know where this virus came from. We may never know what triggered the global pandemic that has claimed more than 3.8 million lives. And we won’t know the long-term effects until enough time has elapsed. What we do know for certain is that the incredible strength and collaboration of the scientific community have allowed us to regain some semblance of normalcy. The development and rollout of multiple effective vaccine options have been the medical miracle of our lifetime.

That, right now, will have to be the only answer that matters.

References
Identifying Promise

In May 2021, the European Commission (EC) proposed a strategy on COVID-19 therapeutics for the European Union (1), which complements the already working EU Vaccines Strategy (2). This therapeutics strategy was aimed at supporting the development and availability of treatments for COVID-19, including ‘long COVID’, and just over a month after it was announced, the EC has already confirmed delivery of its first outcome (3).

So far, the commission has identified five promising candidates as COVID-19 therapeutics that are all already in advanced stages of development. “We are taking the first step towards a broad portfolio of therapeutics to treat COVID-19. Whilst vaccination is progressing at increasing speed, the virus will not disappear, and patients will need safe and effective treatments to reduce the burden of COVID-19,” said Stella Kyriakides, commissioner for Health and Food Safety in a press release (3). “Our goal is clear, we aim to identify more front-runner candidates under development and authorize at least three new therapeutics by the end of the year. This is the European Health Union in action.”

Promising candidates
The five candidates identified by the EC will be prioritized for review, and it is hoped that three of the therapies will gain authorization by October 2021, permitting the final data demonstrate safety, efficacy, and quality. Four of the products identified are monoclonal antibodies, which are already under rolling review by the European Medicines Agency (EMA), and the fifth product is an immunosuppressant that is already authorized for use but would require an extension of use to incorporate COVID-19 treatment.

Eli Lilly’s baricitinib—already approved as Olumiant as a treatment for rheumatoid arthritis and atopic dermatitis—is the immunosuppressant being considered for an extension of marketing authorization for COVID-19 indication. The monoclonal antibodies under rolling review are the combination of bamlanivimab and etesevimab (Eli Lilly), the combination of casirivimab and imdevimab (Regeneron Pharmaceuticals and F. Hoffman-La Roche), regdanvimab (Celltrion), and sotrovimab (GlaxoSmithKline and Vir Biotechnology).

A broader future
Next steps for the commission are to broaden out the pool of potential candidates to 10 therapeutics by October. These therapies will be selected with the help of an expert group on COVID-19 variants—a high-level group on the health emergency preparedness and response authority (HERA) and HERA incubator—that was formed earlier in 2021 (4).

The selection criteria for the broader portfolio of therapies will be defined by the HERA expert group and will be agreed with the EU member states. Product categories will be identified by the working group and then the most promising candidates from each category will be selected so that it will be possible to map out the continuous development of a diverse range of therapies in a dynamic fashion. It is also hoped that the broader portfolio will provide treatment options for different patient populations and different stages and severity of disease.

Depending on research and development outcomes, EMA should start further rolling reviews of other promising therapeutics by the end of 2021, the commission revealed (3). Furthermore, to ensure supply can meet demand in the cases of potential approvals, the commission is holding a virtual matchmaking event in July (5). The event will bring together stakeholders across the whole EU COVID-19 therapeutics value chain with the aim of accelerating the development and upscaling of COVID-19 therapeutics.

References

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he structure and activity of complex biotherapeutic molecules require sensitive analytical technologies that can characterize these complicated protein structures and observe their pharmacokinetic activity, elements fundamental to biotherapeutic drug development and production. Relevant technologies are needed to make detailed analytical assessments of structure and function, and further innovation is needed to address the continued challenge faced by the industry.

The problem with complex biological molecules

The structure of biological molecules poses interesting challenges to analytical assessment. Elucidating the purity or structure of a complex biological product often requires methods designed uniquely to the analyte, multiple analytical assays that leverage cross-modal technologies, and orthogonal analytics to differentiate the analyte from a biosimilar molecule, says William Bakewell, research fellow at PPD Laboratories’ GMP Lab.

A fundamental challenge, says Shawn Fitzgibbons, manager, Catalent Biologics, is the large size of biologics materials, and, in turn, the micro-heterogeneity observed with respect to each attribute measured. “Every molecule will have unique characteristics, for example, although characterization of post-translational modifications is routinely addressed, there may be a specific challenge if the molecule has a high level of modifiable residues at, or near, important binding regions of the molecule, or if the molecule is particularly prone to these modifications because of its given formulation,” he says.

Challenges with respect to functional analyses often revolve around proper, timely, development of the necessary cells and antibodies, Fitzgibbons adds. Similarly, extractables and leachables assessments require a large panel of extraction and analytical techniques to be undertaken to assure detection, identification, and quantitation of a potential toxic, unknown material.

Meanwhile, structure-function assessments have been known to be challenging because the amount of material available to address all orthogonal methods is often limited, says Pedro Morales, director, Catalent Biologics. “For example, it becomes challenging to isolate and analyze variants that are present in only small amounts within the fractionated sample,” he says.

Morales also explains that the extraction and/or purification of variants needs to be done while avoiding the introduction of additional—or exacerbation of—post-translational modifications (PTMs) or impacting the material so as to create
aggregates. He says that experimental design should include appropriate controls needed for analysis in parallel to the analyte(s) of interest. "It is always challenging to develop a robust functional assay that will ensure a solid structure—function correlation that can be unequivocally determined," he states.

Jana Hersch, scientific consultant, Genedata, adds that correct prediction of how a complex biological will behave in vivo remains the biggest challenge during the development of complex biotherapeutic molecules. She points out that antibody-drug conjugates (ADCs), bispecifics, and even engineered cell-surface receptors, such as chimeric antigen receptors (CARs), rely on the scientists’ ability to assess how these molecules will behave once inside the patient.

"It is important to predict not just whether they bind with the desired affinity and specificity to their target in vitro, but also that they bind in the right tissues, or that they have the appropriate level of clearance from the body to achieve the desired therapeutic effect and cause minimal harm," Hersch says. She also explains that many different versions of a complex biological molecule are often tested in iterative pharmacokinetic and pharmacodynamic analyses before the preferred format as well as the final formulation are selected.

Establishing analytical studies
Campbell Bunce, chief scientific officer at Abzena, emphasizes the point that all drug developers should look to establish the right set of analytical methods and workflows to assess the developability of their individual drug candidate and ensure that those they take forward have a reduced risk of inherent liabilities at an early stage. He states a holistic approach that applies design of experiment principles is recommended to capture a wide range of parameters to focus across several characteristics, such as function, manufacturability, immunogenicity, and safety. "For example, through developability assessment, methods can be applied that will provide insights into the relative stability of the biological molecules and allow them to be ranked against comparators to help select the best lead candidate for development," he says.

Bunce notes that often, novel biotherapeutic candidates are unique with little information that can be drawn on to help develop the right assays and comparative assessment parameters, as can be done with antibodies, where a significant amount of historical data exists. Certain aspects of novel biologic molecules can be pieced together, however, directed by experience-led trial and error to generate developability profiles that lead to better outcomes, he explains.

"There may be occasions where liabilities cannot be designed out using protein engineering techniques and thus, need to be managed through different approaches. Consequently, other mitigating options can be evaluated and applied," Bunce states. Biologics, for example, may be affected by one or more degradation pathways that can be evaluated and addressed through the formulation development process to maximize the stability of the biologic drug candidate.

Because of the complexity of biological molecules, a panel of analytical methods is used to analyze the therapeutic proteins for lot release to ensure consistent product quality, safety, and efficacy, adds Gang Huang, senior vice-president, analytical sciences and clinical quality control, WuXi Biologics. Though enormous work is done in the clone selection and process development stages, it is still expected that a final drug product is composed of a mixture of hundreds to thousands of variants that differ in PTMs and higher order structure, he emphasizes. As a result, state-of-the-art analytical methods have been used to thoroughly characterize various PTMs and degradation pathways of these proteins.

Bakewell notes that mass spectrometry (MS)-based analyses are a critical component of determining primary structure for conjugated proteins, monoclonal antibodies (mAbs), and cell and gene therapy (CGT) products. He further explains that intact mass and peptide mapping-based MS methods allow for confirmation of protein sequence as well as identification of any disulfide bonds, oxidation/deamidation events, glycosylation patterns, and PTMs, all of which are key structural critical quality attributes (CQA). Meanwhile, information about secondary and tertiary structure can be determined through techniques such as circular dichroism, isothermal calorimetry, size exclusion chromatography, and multi-angle light scattering.

"Complementary to these protein-level analyses, sequencing of the products underlying DNA can be performed by Sanger sequencing, capillary electrophoresis with fragment analysis, and next-generation sequencing (NGS) approaches. The depth to which a product is sequenced—including a product’s expressing and non-expressing elements—and the degree to which sequencing results confirm a product’s identity has yet to be standardized," Bakewell adds.

Lessons from mAbs
Fortunately, biopharmaceutical analysis methods have improved since the first mAbs were approved. The most significant change over the past 15 years has been the speed and resolution at which bioanalytical tools are employed, says Christopher Colangelo, biopharma business development leader, Agilent Technologies. The development of porous and/or sub-2-um chromatographic media coupled to ultra-high-performance liquid chromatography (UHPLC), for example, has enabled analytical method runtime to decrease 10-fold from 30–50 mins/sample to 3–5 mins/
sample. Colangelo adds that a key success in many biopharma research labs today is the use of automation solutions in lab workflows. “For example, successful labs effectively use robotic sample preparation, liquid autosamplers, and automated data analysis tools,” he states.

Significant improvements have also been made in the sensitivity, resolution, accuracy, reproducibility, and specificity of analytical methods used to support the release and stability testing of biological drugs, Bakewell emphasizes. Sodium dodecyl sulfate polyacrylamide gel electrophoresis and isoelectric focusing gel electrophoretic methods commonly used for release and stability in the 1980s have been largely replaced by capillary electrophoresis (CE) methods, for example, Bakewell says. “CE methods are deemed superior to traditional gel electrophoresis methods due to their improved resolution and their high degree of reproducibility and robustness,” he states.

Similarly, column chromatographic separation techniques have evolved and improved over time to where, for example, the operating pressures that analytical HPLC/ultra high (UH)PLC columns can tolerate has increased. This has resulted in a concomitant increase in analytical resolution, Bakewell explains. Furthermore, improvements in the quality of HPLC systems and batch-to-batch reproducibility of HPLC columns has led to better and more reproducible analytical methods, while data analysis for chromatographic separations has evolved from using paper integrators to US Code of Federal Regulations (CFR) Title 21, Part 11-compliant analytical software, says Bakewell.

“Over time, the variety of good manufacturing practice (GMP)-compliant analytical methods used to evaluate purity, potency, and stability of biopharmaceuticals has expanded and evolved. These now include multiplex and fluorescent plate reader assays, residual assays for process impurities such as host cell proteins and DNA, and in-vitro potency assays rather than animal models,” Bakewell adds. “Improvements in automation that remove analyst subjectivity for compendia methods such as colour, clarity, particulate matter, sterility, and endotoxin analysis have increased the reliability of these methods.”

More recently, Hersch includes, advanced protein engineering has given rise to synthetic antibody-like molecules, including bispecifics, ADCs, or CARs with an antibody-derived targeting domain. “The analytical methods associated with modern protein design are now nearly always high-throughput and require automation, with researchers routinely screening large panels of molecules in different formats to select the very best candidates for further development. A large amount of data is generated at each step and using sophisticated data management solutions that can handle and structure all the associated data centrally across an organization have become the norm in the industry,” Hersch says.

Morales adds that technology, software, and biological knowledge have evolved in such a way that cell-based potency assays are expected to be more robust and precise by default. “Phase-appropriate validation enables the identification of critical reagents and steps, not only for analytical methods, but also from manufacturing process validations. Cell-based development reports are now an expectation to demonstrate that efforts were made to optimize assay precision,” he states.

Fitzgibbons further adds that advances in characterization have occurred within all areas, from improvements in cell-based functional analysis to detection mechanisms in MS-based solutions involving higher-resolution instrumentation. “In several instances, such as in mass spectrometry, data processing solutions have driven evolution where the large amount of data acquired has required powerful software to process the volume of information present in the analysis,” he says.

One hot analytical topic for biopharmaceuticals over the past few years has been sub-visible particle analysis, including particle counts using microflow imaging analysis and high accuracy products liquid particle counters, says Gary Watts, Analytics Manager at Abzena. “The understanding that particles breed particles potentially leading to drug products failing specifications has led to emphasis on early detection to help de-risk the drug development pathway by identifying and removing the likelihood of any issues further down the line,” he explains.

Huang reinforces how analytical advancement has made significant strides for the sake of biological drug development since the 1980s, noting that advances in liquid chromatography (LC) and CE have had significant impact on biopharmaceutical development by improving method robustness and throughput.

“There was a time when scientists had to identify all peaks in a peptide map using Edman degradation—a tedious task with limited sensitivity and robustness—but now the peptide sequence can be easily elucidated via LC–MS. Beyond this, peptide-based multi-attribute method (MAM) as an emerging technology has the potential to offer enhanced sensitivity and selectivity for the simultaneous detection and quantification of multiple product attributes, even in the quality control (QC) laboratory,” Huang says.

For binding assays, Huang says, surface plasmon resonance and biolayer interferometry technologies have become increasingly promising compared with the conventional enzyme-linked immunosorbent assay binding method and have been used in both biologics development and quality control labs.

**What the industry still needs**

Moving forward, the increasing complexity of biologic modalities in drug development may also lead to analytical needs not yet met by current methods. “The field of complex biologicals is diverse and
expanding rapidly,” says Hersch. “Standardization of analytical requirements for full characterization and quality control of these new modalities is, in some cases, still evolving and represents an important unmet need.”

According to Hersch, unmet need in the industry includes quality control analyses for the newest autologous cell therapy approaches, which must be performed quickly to ensure the shortest possible vein-to-vein time for critically ill patients. “To meet this need, researchers may have to rely more on faster NGS-based methods rather than more time-consuming traditional in-vivo procedures,” she envisions.

In addition, as biologic modalities become increasingly complex (e.g., bispecific antibodies, gene therapies, cell therapies), there will be a continued need to develop methods for characterization of the active biologics’ components, says Fitzgibbons. This development may involve analytical techniques that are only just now becoming widely used. “As new higher-resolution analytical techniques and more hybridization occurs within instrumentation, new opportunities for characterization present themselves,” he states.

One example of instrument hybridization involves the combination of CE techniques with MS, Fitzgibbons says. With hybridization such as this, identification of size or charge heterogeneity profiles becomes much more straightforward, he notes. He also says that analytical instrumentation that automates processes that were previously undertaken manually offers higher throughput and opens the way for new regulatory requirements for analytical characterization.

“Additionally, as the development in viral vector manufacturing progresses, and as new gene therapy offerings are developed, new analytical challenges arise to assure CQAs are understood and controlled,” he adds. Meanwhile, on-line/real-time monitoring of product attributes has gained increasing interest due to advancement in continuous processing for biologics manufacturing in recent years, says Huang. He also adds that a greater level of automation in sample preparation as well as applying MS techniques, such as peptide-based MAM, which has been used in quality control to simultaneously monitor different product attributes, can greatly enhance real-time monitoring and expedite biologics development.

“One gap that needs addressing is industry coalescence in developing standardized methods and reagents,” adds Colangelo. He points out that many manufacturers still develop fit-for-purpose methods for each biotherapeutic, which leads to a continual reinvention of the analytical methods for every new drug product. Bunce points out that capacity is a major issue because all providers are looking to access platforms that can express more material in less volume, while maintaining the sensitivity of the process at scale. “Consequently, the industry needs to ensure that

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made significant strides in managing biopharmaceutical industry has meanwhile, explains that the front is a mindset to be encouraged for the patients. Getting things right up front is a mindset to be encouraged in analytical method development to characterize biopharmaceuticals and reduce risk in the drugs that we develop," he asserts.

Marc Wolman, principal scientist at PPD Laboratories’ GMP Lab, meanwhile, explains that the biopharmaceutical industry has made significant strides in managing logistics and working within critical timelines, which has been especially and recently evidenced by the successful development, production, analysis, and review of new pharmaceutical products in record time to battle COVID-19. "However, we also saw that drug sponsors, raw material and testing reagent suppliers, CDMOs [contract development and manufacturing organizations], CROs [contract research organizations], and regulatory agencies have the opportunity to implement faster, more-efficient means to develop, produce, analyze and review new pharmaceutical products, all while maintaining a critical eye on safety and quality," he states.

For analysis of biotherapeutic product CQAs, the advent of rapid microbiological methods, rapid high-throughput screening methods, rapid release and stability methods—in particular rapid bioassay methods that mimic the in-vivo functionality of the product—are all areas where enhanced turnaround times will be critical to getting new products to market, Wolman emphasizes. "The ability of the industry to meet rapid manufacturing and testing turnaround times will define the success and availability of promising autologous cell-based therapies," Wolman adds. For example, to support an autologous cell therapy, a patient’s cells must be harvested and modified, and the modified cells must be rapidly tested for structure, function, identity, purity, and safety-related CQAs before the patient can be infused with the modified cells. "The analytical testing requires coordination of sample shipping and receipt with critical handling, execution of assays and data review, and quality assurance approval of the samples’ testing report," Wolman explains. "This monumental effort may have a limited timeline of one to two weeks given the short shelf life of the ex-vivo modified cells and the patient’s life depending need to receive the therapeutic."

**Meeting future analytical requirements for novel biotherapeutics**

Novel biotherapeutics are expected to have higher heterogeneity (variants); learning and understanding what these variants are will increase assurance of product consistency, says Pedro Morales, director, Catalent Biologics. He explains that massive genomics and proteomics data will need to be correlated with functionality data to identify what is truly critical to set specifications for release.

As the industry moves gradually towards more personalized biotherapeutics, the ability to craft a biotherapeutic for each patient in real-time becomes more of a reality, asserts Christopher Colangelo, biopharma business development leader, Agilent Technologies.

Decreasing the cost of developing immunotherapeutic modalities, especially those based on CGT approaches, will be essential for their broad adoption, says Jana Hersch, scientific consultant, Genedata. "Innovative digitalization and new manufacturing practices will provide key solutions. New and enhanced digital solutions are already becoming available to support CGTs. Since cell and gene therapies often serve relatively small patient populations, miniaturization with patient-scale manufacturing represents another tangible step towards lowering costs," she says.

"While these technologies predated the therapeutics, mechanisms to manage the data generated from these analytical approaches and to validate the instruments’ software for GMP [good manufacturing practice] testing is lacking. For nucleic acid sequencing, whole genome and single-cell-based sequencing platforms continue to evolve with new, powerful software tools to support data analysis," Marc Wolman, principal scientist at PPD Laboratories’ GMP Lab says.

The methods used to characterize, inform, and select the best biologic drug candidates are becoming more complex, requiring different analytical parameters to be assessed, observes Campbell Bunce, chief scientific officer at Abzena, who reinforces the need for speedy analysis with emerging drug platforms. "Innovative means of applying sophisticated analytics to these complex therapeutics in a fast and efficient way is required to help streamline the manufacturing process to increase the chances of success and preempt or reduce safety risks," he says.

—Feliza Mirasol
As the name implies, subunit vaccines are based on a portion of the infectious agent rather than leveraging the entire virus (killed or live-attenuated). A subunit vaccine usually contains a protein, a polysaccharide, or a combination of both. Because they contain only a portion of the pathogen, subunit vaccines typically have fewer side effects and can be given to a wider group of people, including those with compromised immune systems and chronic health conditions. They typically lack pathogen-associated molecular patterns, however, and thus tend to cause weaker immune responses, requiring the use of adjuvants and possibly booster doses.

The first recombinant protein vaccine was developed for hepatitis B, and many more have been approved. Subunit vaccines formulated as virus-like particles (VLPs) and nanoparticles are in development today. Subunit vaccines work by exposing the body to a piece of a pathogen (virus, bacteria, parasite) that triggers an immune response, according to a spokesperson from Novavax. The company’s NVX-CoV2373 candidate vaccine against COVID-19, for example, uses an optimized version of the full-length spike (S) protein from SARS-CoV-2 as the subunit antigen. This antigen cannot cause disease but is delivered in a way that is read to be recognized and learned by the immune system.

In contrast, genetic vaccines (DNA or RNA vaccines) only take a small part of the viral genetic information that encodes the antigen triggering the immune response, notes Axel Erler, associate director of commercial development with Lonza. RNA vaccines, however, don’t generate a direct immune response, adds the Novavax spokesperson. Instead, they deliver a molecule that must be translated into the desired antigen, which is then recognized by the immune system.

Established production platform

One advantage of subunit vaccines is that their manufacture is achieved using established recombinant technology that is widely distributed in the biopharma world, according to Yves Balmer, head of microbial development services at Lonza. "This technology offers a well-defined technical and regulatory landscape that is readily available and does not require the culture of virulent organisms and their subsequent attenuation/inactivation, which can create safety concerns," he says.

In addition, Balmer notes that the recombinant production of subunit vaccines enables the selection of specific antigens that can be combined in a multivalent vaccine and generate a well-characterized product. Furthermore, production platforms for subunit vaccines are highly adaptable, with exactly the same procedures used to develop and manufacture variant-strain versions for use in scenarios of genetic drift, according to a spokesperson from Novavax.

Highly stable vaccines

One key advantage of subunit vaccines over genetic vaccines is their strong stability profile. Transport and storage can take place at regular refrigeration temperatures, and there is no need for ultra-cold freezers. This feature enables the distribution of subunit vaccines in diverse global locations where -20 °C or -80 °C cold chains are unavailable," Novavax’s spokesperson observes.

Such an ability is not an insignificant factor. "It is critical nowadays to set up resilient supply chains to be prepared for any disruptions such as COVID-19. In addition to having transparent and scenario-based forecasting in place to anticipate risk-based future global demand scenarios, managing cold-chain requirements regarding storage and transportation remains a key capability, especially considering the variety of temperature classes (i.e., cool-chain to deep-frozen, all the way down to liquid nitrogen temperatures),” comments Christian Rochel, head of supply chain for biologics at Lonza’s Visp, Switzerland facility.

Rochel adds that a focus on internal and external supply capabilities,
including multi-site inventory management, remains an important factor to ensure full supply.

**Used in currently approved products**

Unlike novel approaches and emerging technologies for vaccine development that can lead to regulatory challenges regarding demonstration of the safety and efficacy of such vaccine candidates, the development and regulatory pathways to commercialization for subunit vaccines are well established, according to Karen Magers, director of regulatory affairs at Lonza. “Vaccine regulators tend to be conservative, and there is a requirement for providing rigorous, supportive data based on the large intended populations for most vaccines, which often include children,” Magers says.

Protein subunit vaccines are an established technology, adds the Novavax spokesperson, and there are several approved subunit vaccine products on the market. Noteworthy for the company is the fact that a recombinant protein subunit vaccine manufactured using Sf9-derived insect cells, the approach used by Novavax for NVX-CoV2373, was approved in 2013. The investigational vaccine candidate being developed by Novavax, however, is also undergoing rigorous evaluation of its safety and efficacy, along with characterizing the company’s manufacturing processes.

One potential challenge for subunit vaccines is the need to use adjuvants in these formulations to achieve robust/broad immune responses. The issue arises, according to Magers, if a novel adjuvant is introduced. “Regulatory challenges can arise while establishing the safety profile of new adjuvants,” she remarks.

**Development takes investment**

The time and money needed to develop subunit vaccines can pose additional challenges. While development timelines for these vaccines are shorter than those for vaccines based on whole pathogens, subunit vaccine development is still time-consuming. One key hurdle is determining the right antigen. Determining the best dose and adjuvant combinations can also take time, according to the spokesperson from Novavax.

In addition, many specific subunits have unique physicochemical properties, and a tailored process needs to be developed for each, starting at the level of the expression host then moving to process and analytical method development, says Balmer. “This process development for non-platform molecules requires expertise, time, and flexibility in the manufacturing facility,” he adds.

An established technology, subunit vaccines have an approval track record.

The cost of goods for subunit vaccines can be an issue as well. “Recombinant protein technology was initially developed for biopharmaceutical drugs, for which the cost of producing the drug substance was not a critical factor,” Balmer observes. In contrast, vaccines are expected to be affordable considering the need for wide implementation.

An approach to address both issues, Balmer notes, is to develop platform processes that would shorten the development timeline, pre-define the manufacturing facility, and reduce the cost. “An example is the production of VLPs in which the frame remains constant and only the antigenic part is target-specific,” he says. This standardized approach, however, is only successful if the antigenic portion remains limited so it does not impact the production process.

For its COVID-19 vaccine candidate, Novavax had a head start due to its recent experience developing vaccines for the original severe acute respiratory syndrome virus and its NanoFlu candidate for seasonal influenza, according to the company spokesperson. This experience combined with knowledge of the coronavirus’ spike protein and access to the company’s nanoparticle technology and proprietary Matrix-M adjuvant has helped to accelerate development of NVX-CoV2373. Today, Novavax can begin testing a new vaccine candidate in the pre-clinical environment within weeks of identification of a variant of concern.

Many advances in the last decade

The concept of subunit vaccines has been around for decades. Several advances in technology have helped improve their development and manufacture. Magers points to progress in genomics for the identification of vaccine candidates and incorporation of three-dimensional (3D) structure, domain organization, and dynamics of surface proteins analysis into vaccine design as aiding development efforts.

There have also been improvements in subunit vaccine formulation, according to Magers, such as the use of nanoparticles (e.g., ferritin) that self-assemble into microscopic particles that display a protein antigen and the introduction of novel adjuvants (e.g., CpG 1018 used in Hepatitis-B, AS04 [monophosphoryl lipid A, MPL] used in Cervarix, and AS01B [MPL and QS-21] used in Shingrix).

Manufacturing advances of note for Magers include expanding use of different expression systems including mammalian, insect, microbial, and fungal cell lines; incorporation of single-use technologies and equipment and closed systems into manufacturing processes; exploration of continuous manufacturing and quality-by-design approaches; and the introduction of novel analytical methods (e.g., mass spectrometry, particle analysis methods, and development of continuous manufacturing and quality-by-design approaches; and the introduction of novel analytical methods (e.g., mass spectrometry, particle analysis methods, and...
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Formulating Tablets Layer by Layer

Bi-layer tablets are an under-utilized option that can be employed to help reduce treatment burden, but their formulation is more complex than for conventional monolayer products.

Felicity Thomas

The oral administration of drugs has persistently been the preferred route of drug delivery for many years, mainly due to patient convenience and manufacturability of the dosage form. "Tablets are the most stable and used oral sold dosage (OSD) form on the market that allows for drug price reductions while also guaranteeing good production yields combined with patient compliance," asserts Federica Giatti, compression technologist at IMA Group.

However, conventional immediate-release tablets are designed to release an active ingredient shortly after oral administration, which generally means a rapid absorption of drug occurs without any specific targeting of therapeutic action. Various methods have been employed to be able to manipulate the release of APIs in the body, in order to control the therapeutic efficacy of treatments, improve patient compliance, and reduce dose frequency.

Bi-layer tablets have been employed as a means of administering more than one API in a single dosage form to achieve controlled drug delivery. Although these dosage forms can offer key advantages, there are also specific complications and challenges that must be overcome to ensure success.

Benefits of bi-layer tablets
In the modern era, continuous scientific research into disease areas and multi-targeted approaches is opening a wide range of possibilities in pharmaceutical development and manufacturing, Giatti confirms. “The possibility to use bi-layer tablets offers some advantages that must be taken into consideration when developing a combination of two or more APIs in a single pharmaceutical form,” she says.

Some advantages of bi-layer tablets include the option of fine-tuning the availability of each API with the possibility of differentiating their release-times, being able to separate incompatible APIs, prolonging the medicine effect after administration, and reducing the dose frequency, Giatti highlights. For example, she continues, in elderly patients, the high number of tablets or medicines that may be required each day can impact quality of life or can lead to medication errors, so bi-layer tablets can be particularly beneficial for this patient population.

“Bi-layer or multi-layer can provide the delivery of more than one drug in one dose thereby adding convenience,” concurs Anthony Carpanzano, director of R&D at JRS Pharma. “Delivery in separate layers can avoid incompatibilities between the compounds that otherwise could not be prevented in a single monolithic structure. Multiple layers also allow for delivery of the components at different rates and visually, multi-layer tablets provide brand recognition.”

Formulation considerations
Formulating a bi-layer tablet is more complex than for a conventional monolayer tablet as two (or more) suitable granulations must be developed. “Generally, to have a blend suitable for compression, the powder should be free-flowing and uniform in terms of particle size distribution; it should be characterized by particles cohesive enough to lock and hold together but not too much so they can adhere to metal surfaces,” notes Giatti.

“Blend characteristics, such as compactability, flow, homogeneity, and low dustiness—to minimize ‘cross-contamination’ between layers—are important,” agrees Carpanzano. “Flow is especially important for layers two and beyond.”

By guaranteeing the blend characteristics, the final tablet should be uniform and defect-free, Giatti continues. “Compatibility is another crucial characteristic to be considered. If the APIs inserted in the formulation are incompatible, they must be separated in different layers and formulated with dedicated
"release," she says. "Last but not least, the sufficient bonding between the two layers must be guaranteed even immediately after tableting and during storage, packaging, and shipping."

To ensure a stable tablet process, when developing and manufacturing a bi-layer tablet, manufacturers must choose the correct tamping and pre- and main-compression forces, and formulation scientists need to select an excipient that is suitable for direct compression, which will allow for easy flowability, compression, and tableting of the blend, Giatti explains. "The tableting should be performed without any contamination between the two layers," she adds. "[Formulators can improve the chances of being contamination-free] by choosing powder with a coarser particle size that can reduce blend volatility around the machine, and manufacturers assist with dedicated aspiration."

Most of the challenges to overcome when developing a bi-layer tablet pertain to process or equipment issues, emphasizes Carpanzano, but other significant considerations include layer adhesion and layer thickness versus tooling shape—in particular, cut depth.

A greater amount of attention should be focused on the bonding between the two layers, asserts Giatti. "From a manufacturer point of view, this [bonding issue] can be solved by applying a slight tamping force in the first layer, whereas for formulators the inner features of all the excipient and APIs present (crystalline habitus, real density, particle size distribution) should be taken into consideration from the beginning," she says.

But, for Giatti, the most significant challenge to overcome is in relation to incompatibilities of the ingredients. "Different release profiles and physical separation of the APIs should be ensured by choosing the relevant type and percentage of excipient(s) or manufacturing technology to use," she states.

Additionally, the development of technologies designed for the compression of multilayer tablets has matured with systems now at the point of simply needing ‘fine-tuning’, reveals Carpanzano. "More development of compression coating or ‘tablet-in-tablet’ is ongoing," he adds.

Software is available that can help developers in choosing the correct formulation, such as IMAGO (IMA Group), highlights Giatti. "This software consists of an instrument that acquires the data of the cells mounted in the machine, such as pre-main compression and ejection force, as well as tablet characteristics (weight, thickness, diameter, and tablet strength) to consider powder behaviour," she explains.

Other software exists that guide the choice of ratio and type of excipient, such as ZoomLab by BASF. Giatti continues. "The combination between these aids and the experience of the supplier and manufacturer can improve and facilitate the choices of the formulators," she says.

**Excipient selection**

"Excipient selection for bi-layer tablets is as important as it is for single-component tablets, and there are instances when it is most important," Gernot Warnke, global head of R&D at JRS Pharma stresses. "For example, when running a high-speed tablet press, the filling of the die with the blend to be compressed occurs when the die passes below the feed frame and the lower punch is drawn downward. This downward motion happens quickly and creates a degree of suction which aids in filling the die. This suction helps to compensate for materials with less than optimal flow in achieving uniform die filling and ultimately consistent tablet weight uniformity."

However, Warnke warns, for multi-layer tablets, the benefits of the downward motion of the punch are only achieved for the first or lower layer of the tablet. "Any subsequent layers must rely solely on blend flow to fill the die cavity. It is therefore imperative to select excipients that impart the best flow characteristics to provide adequate flow characteristics to subsequent layers," he says.

Selecting the optimal excipient for the first layer is also important to ensure the surface, after tamping, has a rough enough porosity to allow for adequate adhesion of the second layer, continues Warnke. "It has been shown that if the first layer is too smooth (due to makeup or excessive tamping) the second or subsequent layer will not adhere well and layers may separate with minimal agitation (i.e., during ejection, discharge, packaging, or over the shelf-life of the product)," he says.

"Due to the fact that the first layer [in a multi-layer tablet] is generally subjected to low compression forces, the formulation should be able to cope with further compression in the second phases of tableting without leading to a fragile tablet," adds Giatti. Furthermore, selecting an excipient with good compressibility can improve the overall tableting output and help to overcome the potential problem of later separation and delamination and capping, she notes.

"To conclude," continues Giatti, "the flowability of the formulation of the first and second layer should be good enough to not generate any issues during the feeding of the tablet press that could cause a reduction of output or [overall equipment effectiveness] of the manufacturing equipment."

**Regulatory factors**

Widely encompassing regulatory factors are to be considered when approaching bi-layer tablets: following the correct good manufacturing practice approach to ensure a high-quality tablet is produced that complies with the standard customer specifications and pharmacopoeial requirements, specifies Giatti. "At the same time,
Development

Subunit vaccines (Contin. from page 14)

Capillary electrophoresis (CE) in conjunction with an emphasis on replacing in-vivo potency assays. Since the first subunit vaccine was approved for hepatitis B, Novavax has advanced the technology for this class of vaccines through its use of a nanoparticle core to present the protein subunits to the immune system in a way that results in robust, durable responses that offer protection in the face of genetic drift, according to the company’s spokesperson. In addition, evaluation of Novavax’s vaccine technology has also revealed additional uses for its proprietary Matrix-M adjuvant when paired with vaccine antigens developed by other organizations.

Combination subunit vaccines are also now being explored, such as Novavax’s NanoFlu + NVX-CoV2373 candidate, to address multiple infectious disease threats. This investigational combination subunit vaccine, which is made possible by technology that is flexible, uses very low amounts of antigen, and is combined with an adjuvant that shows an encouraging safety profile, has already shown strong results in pre-clinical evaluations, according to the Novavax spokesperson.

Role to play in the fight against COVID-19

More than 20 protein subunit vaccine candidates have entered clinical trials for COVID-19, including those from Novavax, Anhui Zhifei Longcom Biopharmaceutical, Kentucky Bioprocessing, and Sanofi/GlaxoSmithKline, among others. More than 50 other candidates are at the preclinical stage.

More than 20 protein subunit vaccine candidates have entered clinical trials for COVID-19.

“We believe that whether by providing best-in-class efficacy as a primary immunization series or boosting those previously vaccinated with our or another vaccine, subunit vaccines promise to be a vital part of the global effort to fight the COVID-19 pandemic. With a cold chain that does not require freezing, these vaccines will likely be delivered and used around the world,” states Novavax’s spokesperson.

In the Novavax NVX-CoV2373 candidate, the spike protein is organized around a nanoparticle and formulated with Matrix-M adjuvant. This technology platform using the full-length spike protein with Matrix-M adjuvant has, according to Novavax’s spokesperson, delivered outstanding efficacy against the original COVID-19 virus (96.4% in a United Kingdom Phase III clinical trial), protection against variants, and a favourable safety profile. In mid-June 2021, the company reported 90.4% efficacy overall from a Phase III trial in the US and Mexico.

“Organizing spike proteins around a nanoparticle core enables the immune system to learn different facets (epitopes) of the spike protein, including cryptic/hidden epitopes, which we think helps to explain the strong clinical results from our Phase I, II, and III studies,” Novavax’s spokesperson adds.

In addition, Novavax has established a global manufacturing network to increase its capacity to respond to infectious disease threats, including COVID-19. In announcing the latest clinical trial results, the company said it plans to file regulatory authorizations in the third quarter of 2021 after it completes final phases of process qualification and assay validation needed to meet chemistry, manufacturing, and controls requirements (1).

Reference

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Formulation of Modified Liquid-Solid Compact for Dissolution Enhancement of Raloxifene Hydrochloride

Gayatri Patel, Dharmang Pandya, Pushti Gandhi, and Rajesh Parikh

Raloxifene hydrochloride (RLX), used in post-menopausal osteoporosis, is a class–II drug as per Biopharmaceutics Classification System. The purpose of this research was to formulate modified liquisolid compacts (MLSC) of RLX for improved dissolution in immediate-release tablet formulations. Preliminary trials on selection of excipients were performed. Fourier transform infrared spectra illustrated no interaction between drug and MLSC powder. The X-ray diffraction studies demonstrated the transformation of the crystalline nature of drug into partial amorphous state in MLSC. After all experimental results on selection of excipients were analyzed, the final tablet formulation was derived and manufactured. The results of an in-vitro drug release study from the selected batch illustrated a remarkable improvement in the dissolution rate as compared to reference product. An accelerated stability study as per the ICH Q1 (R2) guideline of the optimized batch was performed for six months and showed no significant change in critical quality attributes of formulation.

Materials and methods

Materials. RLX was received as a gift sample from Cadila Pharmaceuticals. Other materials obtained were propylene glycol (PG) and Tween 80 (Merck Specialities); polyethylene glycol (PEG) 400 and PEG 600 (Loba Chemie); Capmul MCM 30 (Abitec); capryol 90, lauroglycol, and Labrafil (Gattefosse); Avicel

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Pharmaceutical Technology Europe JULY 2021 21

101 and 102 (FMC Biopolymer, Ireland); Avicel112 (FMC Biopolymer, Belgium); Aeroperl 300, Aerosil 200, and Aerosil 300 (Evonik Industries); and Kyron T 314 (Corel Pharma Chem). Other tabletting excipients were obtained from SD Fine Chem. All other reagents used were also of analytical grade.

Methods. MLSC system comprises non-volatile liquids, solubilizer, carrier material, coating material, matrix pore former, and other suitable tabletting excipients. The following sections describe the method for selection of suitable excipients for MLSC system (17,18).

Selection of non-volatile liquid and solubilizer other than non-volatile liquid. Solubility method was used to select the suitable non-volatile liquid. In this method, solubility of RLX was determined in selected non-volatile liquids (PEG 400, PEG 600, Glycerin, Tween 80, Labrafilm, Capryol 90, Capmul MCM30, Lauroglycol, PG, and blends of non-volatile liquids, in 5-mL total volume of each). TPGS 1000 (d-α-Tocopheryl polyethylene glycol 1000 succinate) in a concentration range of (0.5–2% w/v) and polyvinylpyrrolidone (PVP) K30 in a concentration range of (1–3 %w/v) were selected as additional solubilizers based on the reported literature.

Selection of carrier. Binding capacity method was used to select a suitable carrier for the liquid blend. Avicel PH101, Avicel PH102, Avicel PH112, dicalcium phosphate, and lactose monohydrate were selected as carrier materials. Addition of 0.1 mL of liquid blend to 1 g of carrier material was continued until a satisfactory range of Carr’s index was attained.

Selection of coating material. Aerosil 200, Aerosil 300, and Aeroperl 300 were used as coating materials. The coating material that helped the powder blend to exhibit the lowest Carr’s index was selected.

Preparation of MLSC. MLSC batches were prepared as per the method shown in Figure 1. Tablets were prepared using a rotary tablet punching machine under constant pressure by direct compression procedure using 10-mm diameter, flat punches.

Evaluation of parameters. Pre-compression studies of MLSC, the flow property of MLSC was estimated by determining the Carr’s index (19).

Post-compression studies for the MLSC tablet. For drug content, 20 tablets were weighed and powdered. An amount of powder (each tablet contained RLX 60 mg) was dissolved in 100 mL of methanol, filtered, and analyzed for drug content at 287 nm using an ultraviolet-visible spectrophotometer (UV-Vis) (20). A compendia method was used to determine the uniformity of weight and disintegration time (21). A Pfizer hardness tester was used to determine hardness, and a friability tester was used to measure the friability (22).

In-vitro dissolution study. Dissolution studies were performed for prepared MLSC tablets using a dissolution test apparatus (EDT08, Electrolab) in 900 mL pH 1.2 acidic buffer maintained at temperature 37 ± 0.5 ºC. A type–II (paddle) apparatus was used with stirring rate of 50 RPM. The sampling time was set at intervals of 0, 15, 30, 45, 60, 75, and 90 minutes. At each time interval, a 5-mL sample was withdrawn using a pipette fitted filter. The sample was diluted suitably with pH1.2 acidic buffer, and absorbance was measured at 287nm using UV-Vis (13) (22).

**Equation 1**

\[
\text{Equation 1}
\]

**Figure 1.** Method for preparation of modified liquid solid compact (MLSC) tablet. PG is propylene glycol; PEG is polyethylene glycol.
was used to calculate the concentration of RLX present in the sample where absorbance was measured.

\[ y = 0.0909x + 0.0237 \]  \hspace{1cm} \text{[Eq. 1]} \\

Where \( y \) = Absorbance, \( x \) = Concentration of RLX in the sample (\( \mu \text{g/mL} \)).

The amount of RLX dissolved in dissolution medium was calculated from Equation 2.

Amount of RLX dissolved (mg) (a) = \( \frac{x \times \text{dilution factor}}{1000} \) \hspace{1cm} \text{[Eq. 2]}

The percentage of RLX dissolved was calculated from Equation 3.

% RLX dissolved = \( \frac{a \times 100}{60} \) \hspace{1cm} \text{[Eq. 3]}

The dissolution efficiency (DE %) of the optimized formulation was calculated in comparison to API and marketed product using Equation 4 (23).

\[ \text{DE} \% = \left( \frac{y}{y'_{100}} \right) \times 100 \] \hspace{1cm} \text{[Eq. 4]}

Where \( y \) = time duration, \( y'_{100} \) = time for 100% release, \( dt = t_2 - t_1 \) final time duration- \( t_1 \) initial time duration.

**FTIR study.** FTIR spectra of pure drug and optimized formulation were recorded by the potassium bromide pellet method using an FTIR spectrophotometer at a resolution of 0.15 cm\(^{-1}\) with wavelength of 4000–400 cm\(^{-1}\) and 20 scan sec\(^{-1}\) scanning speed (24).

**X-ray diffraction (XRD).** XRD patterns were studied for pure drug and optimized formulation using an X-ray diffractometer. Samples were exposed to 1.540\(^{\circ}\) A Cu radiation wavelength, voltage 3kV, and scanning speed 4\(^{\circ}\)/min and analyzed over the 20 range of 0–801 (24).

**Accelerated stability study.** Samples were packed in aluminium foil and sealed appropriately to mimic final packaging. Stability studies were carried out as per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline Q1(R2) and analyzed for critical parameters (25).

**Results and discussion**

Experiments were done to select the optimal type/grade and amount of suitable excipients to get a formulation with desirable dissolution properties. The following sections describe the results of the evaluation of the suitability of excipients for the MLSC system.

**Selection of non-volatile liquid.** Figure 2 describes the results of solubility studies of RLX in non-volatile liquids. From the results, the highest solubility of drug was observed in PG followed by PEG 600, as compared to other selected liquids.

Further solubility studies were carried out on selected blends of liquids in the equal ratio (50:50), and these studies concluded that the highest solubility was in the PG:PEG 600 blend (Figure 3).

Further solubility studies were carried using selected blends (PG with PEG 600) in different ratios. The PG:PEG 600 blend having equal proportions showed the highest solubility and was selected for further study.

Modification in an LSC system was carried out by addition of selected solubilizers; solubility study results are summarized in Table 1.

The highest solubility was in solvent system 7 (equal ratio of PG:PEG 600 in the presence of 1% TPGS and 2% PVP K30); this system was selected for further study.
Selection of carrier and coating material. Avicel PH101 was selected as carrier material as it shows the highest binding capacity (3 mL/g) and acceptable flow properties. Aeroperl 300 was selected as coating material and exhibited good flow characteristics amongst all selected coating material.

Selection of superdisintegrant. Four superdisintegrant sodium starch glycolate (SSG), Neusilin US2, cross-Povidone (CP), and KyronT-314, were selected for tablet preparation, and disintegration time was measured. The results are shown in Table II.

After all experimental results on selection of excipients were collected, batch RDMLSC3 was chosen as the optimized batch for further evaluation.

Physicochemical characterization of optimized batch. Carr's Index (%) (n = 3) was found to be 10.00 ± 1.04, which indicates good flow properties of the prepared blend for further compression. The selected batch met the requirement of an ideal pharmaceutical tablet including weight variation, hardness, friability, disintegration time, and content uniformity. All parameter results were interpreted with standard limit and found to be within acceptable limit.

In-vitro dissolution study. A comparative in-vitro profile of drug dispersion, reference product (Ralka 60 mg Tablet, Cipla Ltd.), optimized MLSC, and LSC batch is presented in Figure 4. From the results, statistically significant differences were observed for all samples. Complete dissolution was observed at 45 minutes in the MLSC batch, while for others, it was extended to more than 90 minutes. The dissolution efficiency (DE) of the reference product was 12.5% higher in comparison to API; whereas for optimized batch, it was 40% higher in comparison to API. It is evident that there was a 3.2 times increase in DE % of the optimized batch when compared to the reference product.

FTIR and XRD study. FTIR spectra of the drug and the optimized batch are shown in Figure 5, which shows the retention of all functional peaks of drug at the same intensity in the formulation. The XRD pattern in Figure 6 indicates the crystalline nature of drug. In the present study, reduced crystallinity of drug in MLSC indicates solid state interaction of drug with additives used in formulation and suggests the enhanced dissolution of drug (26).

Stability study. From the results of six months of accelerated stability data, the optimized formulation of RLX was found to be stable with reference to critical quality attributes, such as physical appearance, hardness, and drug content. An in-vitro drug dissolution study of the optimized batch in pH 1.2 acidic buffer at 0, 1, 3, and 6 months, shown in Figure 7, suggests no statistically significant differences (p > 0.05) in drug release data for a period of six months. XRD study of the stability sample after six months shows no changes in initial pattern of MLSC.

Conclusion

The MLSC technique has been used for improving dissolution of RLX. In this present study, an RLX MLSC tablet was prepared with better dissolution, which may enhance the absorption and bioavailability of the drug in the treatment of osteoporosis. Future work will include a long-term stability study as per ICH guidelines, a clinical study, and pilot-plant scale up.

Table I. Results of solubility studies for selected solubilizers.

<table>
<thead>
<tr>
<th>Solvent system</th>
<th>Composition</th>
<th>Solubility (mg/mL)* (Mean ±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG</td>
<td>PEG 600</td>
<td>TPGS 1000 (w/v)</td>
</tr>
<tr>
<td>1</td>
<td>5mL</td>
<td>5mL</td>
</tr>
<tr>
<td>2</td>
<td>5mL</td>
<td>5mL</td>
</tr>
<tr>
<td>3</td>
<td>5mL</td>
<td>5mL</td>
</tr>
<tr>
<td>4</td>
<td>5mL</td>
<td>5mL</td>
</tr>
<tr>
<td>5</td>
<td>5mL</td>
<td>5mL</td>
</tr>
<tr>
<td>6</td>
<td>5mL</td>
<td>5mL</td>
</tr>
<tr>
<td>7</td>
<td>5mL</td>
<td>5mL</td>
</tr>
</tbody>
</table>

Table II. Composition of RLX modified liquid solid compact (MLSC) prepared using different superdisintegrant.

<table>
<thead>
<tr>
<th>Blend</th>
<th>Ingredients</th>
<th>Composition of each tablet</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>RLX</td>
<td></td>
<td>Drug</td>
</tr>
<tr>
<td></td>
<td>PG: PEG 600 (Blend Non-volatile liquids in 50:50)</td>
<td>0.3 mL</td>
<td>0.3 mL</td>
</tr>
<tr>
<td></td>
<td>TPGS 1000 * (1 % of Non-volatile liquid blend)</td>
<td>3 mg</td>
<td>3 mg</td>
</tr>
<tr>
<td></td>
<td>PVP K30 ** (2 % of Non-volatile liquid blend)</td>
<td>6 mg</td>
<td>6 mg</td>
</tr>
<tr>
<td></td>
<td>Avicel PH101</td>
<td>200 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td></td>
<td>Aeroperl 300</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td></td>
<td>Superdisintegrant*** (3% of Blend A)</td>
<td>SSG 18 mg</td>
<td>CP 18 mg</td>
</tr>
<tr>
<td></td>
<td>Magnesium Stearate ^ (2% of Blend A)</td>
<td>12 mg</td>
<td>12 mg</td>
</tr>
<tr>
<td></td>
<td>Talc ^ (1% of Blend A)</td>
<td>6 mg</td>
<td>6 mg</td>
</tr>
<tr>
<td></td>
<td>Disintegration Time (Sec)</td>
<td>167</td>
<td>232</td>
</tr>
</tbody>
</table>
**References**


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A carrier-based formulation strategy is well known by the inhalation community. Novel formulation requirements, such as the delivery of poorly water-soluble compounds, biomolecules, and high dosages to the lungs, however, are not easily met by the conventional strategy. As a consequence, spray-drying has gained interest as an enabling technology for inhalation drug delivery, culminating in an increasing number of products on the market.

In this article, the use of spray-drying as a platform for tailored dry powder inhaler (DPI) formulation in combination with disposable devices will be explored, for amorphous composite particles with enhanced characteristics and performance, for a diverse range of doses and applications. The main advantages of this manufacturing process for inhalation drug delivery will be discussed in detail as well as the manufacturing challenges and critical process parameters to take into consideration when developing a spray-dried DPI, from particle engineering to device filling.

Pulmonary delivery is a well-researched, non-invasive method for local and systemic drug delivery of APIs. The lungs have unique features, such as large surface area, thin alveolar capillary membrane, low enzymatic activity, and absence of first-pass metabolism, making this route of administration attractive for drug delivery (1). Although there are three major strategies to succeed in delivering drugs to the lung (nebulizers, metered-dose inhalers, and dry powder inhalers [DPIs]), DPIs allow for an immediate delivery without propellants.

DPIs are a combination of device and dry powder capable of delivering, upon patient breathing, APIs to the lung surface. To accomplish this delivery, the device must ensure efficient particle aerosolization, and the formulation should have suitable aerodynamic properties. Amongst DPIs, carrier-based formulations are the most well-known and established. These formulations comprise a physical mixture of large carrier particles and micronized API with optimized size and morphology (2). Fine particles of excipients might be added to these mixtures to improve the aerodynamic performance of the drug product.

**Carrier-based formulation challenges**

Carrier-based drug products present some advantages, namely improved stability as a result of the dry crystalline state and a robust manufacturing process. These formulations, however, have some drawbacks, such as an inefficient drug deposition in the deep lung; in fact, it is estimated that only 10–15% of the drug administered reaches the deep lung, as about 20% of the drug administered is lost in the oropharyngeal tract and the remaining percentage is not released from the carrier (2, 3). Delivery efficiency is especially hindered on the delivery of higher dosages; as the drug load in the blend increases, the aerodynamic performance decreases, proportionally (4). Another limitation of these formulations is the inability to act as a solubility enhancer for poorly water-soluble compounds; it is not the main purpose of carrier-based formulations to modify or improve the surface of the API and consequently, its dissolution rate. Lastly, carrier-based formulations require a micronization step, which makes its applicability to sensitive compounds, such as biopharmaceuticals, challenging. The molecular weight of biologic molecules under development for inhalation ranges from a few kDa to about 50 kDa. Larger molecules present increased difficulties when developing a formulation for inhalation, given the increased likelihood of chemical and physical stability challenges (5).

**Role of particle engineering**

A new formulation strategy reveals a promising and innovative way of increasing the pulmonary deposition of drugs. Spray drying (SD) is the gold standard particle engineering technology usually employed in the manufacturing of engineered particles in which the API is
alone or embedded within an excipient matrix (6). SD enables the production of inhalable powders with increased control over particle size, morphology, and density by fine-tuning formulation composition and process parameters.

Particle engineered formulations produced by SD have an optimized aerodynamic performance, leading to an increased fine particle fraction (FPF), meaning a higher delivery to the deep lungs. The optimized performance of carrier-free particles is due to the intentional particle design, as well as better powder uniformity and aerosolization (3). Particle design upon SD is achieved by the association of ingredients with different roles within the same powder, and by adjusting the SD process parameters, leading to different particle morphologies and interactions. As a consequence, the SD technology enables a reduction of the API concentration in the formulation while maintaining the amount delivered to the target (7). Additionally, amorphous solid dispersions manufactured by SD are extensively used for solubility enhancement for other delivery routes and have shown similar results on pulmonary delivery (8). Another SD application is the stabilization and effective pulmonary delivery of biopharmaceuticals within composite engineered particles, while preventing product denaturation at high temperatures due to the flash-drying phenomenon (5).

**Challenges during composite particles development**

In spray drying, both a feed solution and suspension can be processed. The feed is atomized in a nozzle into a fine spray which is typically flash dried by a co-current stream of hot nitrogen. The particles, once formed, are collected in cyclones and/or bag filters and the drying gas recycled after condensing the removed solvent.

There are a limited number of excipients suitable for lung delivery, and excipient choice is driven by stabilization of the API, which translates into stabilizing the amorphous form of an API or decreasing the mobility of a biomolecules, improvement of formulation dispersibility by adding a shell former to maximize aerodynamic performance, and, if required, permeability enhancement by adding a lipid for instance (3). Consequently, to take advantage of the SD technology during the preparation of composite particles for inhalation, it is mandatory to perform adequate excipient selection (9).

The SD technique enables the production of inhalable particles with controlled particle size, water content, morphology, and density by tuning not only the formulation composition, but also the process parameters. There are several phenomena to take into consideration in the SD process: the atomization that is key for determining the droplet size and, later on the particle size; the particle formation, with the process drying kinetics impacting particle size and morphology; the overall fluid dynamics across the equipment, dictating drying efficiencies and overall yields on the collector, as well as the overall process (3,8). Adequate process development and adjustment of process parameters allow a tight control in the powder characteristics and an improvement of powder uniformity, dispersibility and, consequently, aerosolization behaviour. This process development ultimately results in a drug product with an augmented delivered dose to the lungs, without increasing the emitted dose, which benefits the overall safety of the drug product with a reduction in the adverse side effects experienced by patients with respiratory diseases. Furthermore, from the manufacturer’s point of view, SD technology represents an easy to operate, flexible, readily scalable, and time-effective technology (9).

**Case study**

As a case study, consider the DPI development of a synthetic peptide AP301 (Solnatide) designed to activate the epithelial sodium channel (ENaC) of type II alveolar cells of lungs. Solnatide requires a high dosage delivery to clear pulmonary edema arising, for example, from high altitude exposure, blood transfusions, or lung infections (e.g., pneumonia and influenza) (10).

The SD process development targeted a drug-alone product (i.e., free of additional excipients) suitable for lung delivery. The goal was to obtain different particle size distributions (PSD) aiming to reduce the adhesive/cohesive forces that are typically present in composite particles.

A disposable, prefilled device (TwinMax, Hovione), which was designed to handle high dosage delivery of challenging powders, was used. Three device prototypes were studied, with the aim of maximizing the dispersive forces and powder deagglomeration. A prefilled device (as opposed to a capsule-based DPI) is an advantage for rescue/emergency treatments. Since the device is prefilled, the cohesive/adhesive balance must be fine-tuned and optimized to have lower adhesion to the device as well as lower attachment to the coarse lactose, aiming for an increased fine particle mass (FPM).

The engineered particles were manufactured using a Büchi unit model B-290 Advanced, by spraying a solution of the API (AP301) in water. The atomization ratio was optimized to refine the PSD and to optimize the cohesive-adhesive balance between particles and devices’ surface (see Table I).

The results in Table I show that the manipulation of the ratio of atomization allowed a fine control of the PSD (with all Dv50 values comprised between 2 and 3 μm). All powders were found to be amorphous, with a very high purity and a low water content (KF < 5%). All powders presented bioactivities comparable with the starting raw material (SRM), indicating the SD process does not lead to degradation or loss of function.
The batches obtained were characterized in terms of their aerodynamic performance using an Andersen Cascade Impactor, with TwinMax prototypes operating at ~40 L/min for 4 kPa. The parameters analyzed were emitted mass (EM) (mg) and FPM (mg). A total of three replicates were carried out to characterize the selected combination of powder and device shown in Figure 1.

The results reveal that the strategy of improving the aerodynamic performance through particle size manipulation was fruitful. Comparing batch 1, 2 and 3 filled in TwinMax, a dependency of aerodynamic performance on particle size can be observed; batch 2 (larger particles, Dv90 of 5.9 μm) result in a DPI with a significantly higher EM, while the remaining formulations present a higher retention on the device surfaces upon actuation. Additionally, FPF is inferior for batch 1 (smaller particles, Dv90 of 3.9 μm). This result can be explained by the increase of surface area with the decrease of particle size, leading to more significant particle agglomeration, and more energy required to deagglomerate. It is important to note all batches are within the inhalable range, and the dependency is expected to be inverse for larger particle sizes, as the FPM would decrease. Comparing the results of the batch 3 filled into the three prototypes, prototype 1 presents superior performance. The combination of Batch 3 and TwinMax 1, with a Dv90 of 4.9 μm, yielded an EM of 80 mg (a 15% increase when compared with Batch 1). Overall, these results suggest that a compromise between PSD, EM, and FPM should be considered, since higher PSD lead to higher EM but, in general, to lower FPM as a consequence of a different balance between cohesive and adhesive forces. Additionally, TwinMax 1 was the most promising device, with a FPM above 30 mg, which is a high result considering the prototype nature of the device.

### Conclusion

In conclusion, SD technology enables the production of inhalable particles with improved characteristics, such as controlled particle size, morphology, and density. This control is possible through fine-tuning of formulation composition and optimization of process parameters, such as the solvent system, solute concentration, atomization, feed flow-rate, drying gas rate, and others. The protein AP301 spray-dried powder in combination with the TwinMax device shows how SD can be applied to design a high-dosage, stable DPI containing a biopharmaceutical, with adequate aerodynamic performance and without affecting the molecule bioactivity.
Prefilled syringes continue to evolve to enhance operation, support increased automation of the fill/finish line, and boost productivity and output. Syringe innovations also increase patient and caregiver safety and efficiency and reduce waste of product and packaging materials. “Since it is already packaged ready for the injection, the prefilled syringe saves time and avoids unneeded handling prior to the actual application, minimizing the risk of the injection errors, dilution errors, or non-sterility issues [that are a risk in] multi-dose containers,” explains Wenzel Novak, global senior director of business development at Gerresheimer Medical Systems.

Novak estimates that prefilled syringes currently account for 10–15% of the parenteral market and anticipates rising demand. A market study by Emergen Research predicts sales of prefilled syringes will expand at a compound annual growth rate of 8.9% between 2019 and 2027 to nearly double in value to €7.7 billion (US$9.11 billion) in 2027 (1). Driving forces include vaccine production as well as the adoption of self-administered biologics for chronic conditions such as diabetes and auto-immune diseases (1).

“If you look at the top 40 injectable products, all are being used with prefilled syringes,” reports Dr. Nicolas Brandes, director of product management, Polymer Prefilled Syringes and Vial Containment at West Pharmaceutical Services.

Prefilled syringes can be made of glass or plastic such as cyclic olefin polymer/cyclic olefin copolymer (COP/COC) or polypropylene (PP). Glass dominates in most markets. Novak predicts, however, that the share of co-injection-molded COP/COC prefilled syringes will grow from 2% to more than 5% during the next decade.

“We have seen more approvals for products in plastics especially during the past five years,” reports Brandes. He notes plastic syringes often are chosen for specific applications such as contrast imaging agents, hyaluronic acid, and Botox as well as for products that are sensitive to silicone oil. Plastic syringes also function well in auto-injectors.
needs too. "Smaller, thinner needles mean less pain," he explains.

User-friendliness is the goal behind a collaboration between Gerresheimer and Stevanto Group whereby Stevanato supplies its ITC twist-off closure system for Gerresheimer’s Gx RTF luer lock syringes. The integrated seal cap consists of an elastomeric component, which is available in different formulations, and a rigid, translucent polymer cap. Advantages include greater stability and shelf-life protection versus traditional luer cone systems (2).

Prefilled syringes offer sustainability benefits by eliminating multi-dose vials and related production and handling as well as product waste associated with leftover product. Still, says Brandes, "there’s a lot of room for improvement. Current systems create a lot of waste." But efforts are being made to reduce scrap rates and to recycle tubs that hold nested containers during the fill/finish process.

To meet the priority of product safety, suppliers seek designs to prevent needlestick injuries and to protect product quality by minimizing particulates and eliminating product interaction with tungsten or silicone residues. For tungsten-sensitive products, Gerresheimer Biological Solutions offers a metal-free manufactured syringe. With this patented technology, the pin used for conical shaping is made of a ceramic rather than tungsten or another metal.

Silicone oil is commonly used to facilitate syringe performance but can cause aggregation and particulate problems for sensitive biologics. “There’s a push by ophthalmologists and regulatory bodies to move away from siliconized formats,” reports Brandes. “Some patients have reactions to silicone, and over time with repeated injections, the material can accumulate [in the eye],” he explains.

One silicone-free option combines Improject plungers from W.L. Gore & Associates with syriQ BioPure silicone-free syringes from SCHOTT. The system opens the door for many sensitive products to move into the prefilled syringe format. Until the advent of a silicone-free design, "Pharmaceutical manufacturers seeking to avoid silicone-induced aggregation and sub-visible particles have had to choose vials even when they wanted to offer other delivery options," said Christiane Gumera, product specialist at W.L. Gore & Associates. Careful attention to syringe geometry and dimensions of the syriQ BioPure syringes helps ensure a consistent gliding force and injection duration over the shelf-life of the product and maintains container/closure integrity without the use of silicone. Ultra-low tungsten residuals and minimal cannula adhesive residuals further reduce the extractible profile and the risk of container/drug interactions (3).

To prevent potentially hazardous accidental needlesticks and comply with regulations in various parts of the globe, some syringes like Gerresheimer’s InnoSafe product incorporate a pre-applied, passive safety device. With the pre-applied device, there’s no need for post-filling assembly equipment or for healthcare professionals to install a guard before an injection is given. Advantages include improved compatibility with auto-injectors and a completely hidden needle that gives patients with needle-phobia a better experience. The design also prevents accidental reuse and runs on existing fill/finish lines without any additional equipment or process steps.

Finally, COVID-19 has spurred the development of prefilled syringes, particularly with regard to low-temperature storage. Brandes predicts, “Right now all COVID-19 vaccines are in vials, but in the next two to four years we will see a novel type of syringe that handles -80 ºC.”

Fill/finish innovations
Innovations on the fill/finish line focus on automation and flexibility for higher output, greater efficiency, and faster return on investment. As batch sizes shrink, demand for flexibility rises. Brandes explains, “Flexibility makes it possible to fill a batch of 10,000 units in vials and then switch to a different packaging format and drug on the same line. There’s no need to invest in separate lines for vials, cartridges, and syringes.”

Driving forces behind automation include consistency, regulatory needs, and labour requirements. “Automation greatly increases consistency and decreases the possibility for human error, and also can provide opportunities for enhanced inspection capabilities—including those that consider visual attributes, weight, and fill volume,” says Deborah Smook, vice-president of Marketing & Business Development at TurboFil Packaging Machines. She notes, "[United States Food and Drug Administration (FDA) preferences are another consideration. FDA prefers less—ideally no—touching of syringe components for aseptic filling/processing. Finally, automation decreases labour requirements, diminishes the difficulties of working in a cleanroom with full personal protective equipment, and reduces the likelihood of repetitive motion injuries.”

A €42-million (US$50-million) expansion at Baxter Biopharma Solutions in Bloomington, Ind., will boost efficiency and enhance product quality with the installation of a high-speed automated syringe fill line capable of handling up to 600 units/ min and other improvements (4). A fully automated debagging system for RTF syringes has been installed on the newest fill line, and an automated inspection machine has replaced an older system. “[Secondary] packaging lines also feature new packaging options that are plastic-free, as well as tamper-evident,” reports Wendy Saffell-Clemmer, lead scientist and senior director, Baxter. In addition, she says, “Both one-dimensional and two-dimensional online barcode printing is available. Lastly, information technology systems supporting
serialization can communicate with the customer’s system to ensure that the serial numbers applied are unique and traceable across the network of product manufacturing sites the customer may be using.”

The new systems were carefully evaluated with particular attention to prior experience with the instrument manufacturer, anticipated customer requirements, and the available footprint for installation. “New automation technologies were selected to enhance efficiency as well as product quality,” says Saffell-Clemmer. “For example,” she reports, “the newly installed inspection machine has the latest vision systems, which can reduce the false detection rate as well as offer a solution to detect particles in heavy suspension products such as vaccines.”

Civica Rx is building a greenfield, 120,000-ft² aseptic fill/finish operation in Petersburg, Va., as part of a manufacturing partnership with Phlow Corporation, AMPAC Fine Chemicals, and Virginia Commonwealth University’s Medicines for All Institute. The plant in Petersburg will start up with one syringe- and one vial-filling line with space available for another vial or syringe line. The syringe line is rated at up to 50 million units/yr. Isolator-equipped automated fillers with automatic vision inspection are designed to minimize manual intervention and maximize quality, compliance, and assurance levels. Automation “allows the product to be washed and filled at tight tolerances with no human touch,” reports Stan Benson, vice-president and general manager, Civica Petersburg. In-process control and weighing of each syringe before and after filling ensure precise fill volumes. Automatic micro-adjustments maintain fill accuracy throughout the batch. Vacuum-assist stoppering minimizes oxygen levels within the headspace (i.e., the distance between the product and the plunger). The low oxygen levels and small headspace enhance product stability and protect product potency.

All product contact surfaces—from the compounding vessel to the filling needles—are single-use and arrive gamma-sterilized and ready to use. “Single-use systems eliminate the need for clean-in-place and sterilization processes that consume testing and energy [resources],” explains Benson. Each syringe will undergo automated visual inspection to confirm container and closure integrity and fill volume and check for container flaws and particulates. High-voltage leak testing will help check for glass deterioration. On the equipment side, TurboFil Packaging Machines offers several syringe filling options including rotary indexing monoblacks, walking beam fillers, and robot-assisted parts assembly. “Syringe formats are more varied than vials and require a more flexible approach to overcome the challenging filling issues surrounding product viscosity, air evacuation, leakage, and of course, accuracy,” explains Smook.

Employing a versatile yet precise setup that accurately fills syringes via a ceramic piston, peristaltic pump, or direct draw from a reservoir bag, TurboFil’s SimpliFil syringe filling and assembly system handles small to medium batches (see Figure 1). Its walking beam indexing configuration provides intuitive operation and simplified, recipe-based changeover. For heightened precision, TipFil technology allows syringes of all types to be filled through the tip—a step-saving innovation that eliminates the need to insert plungers post-filling. Offering full control of filling parameters in single or dual operation, the benchtop TipFil syringe filler accurately and consistently fills up to 12 units/min. A servo-driven piston mechanism draws the needle back via the plunger, with the distance the plunger is moved dictating the amount of drug filled. Among other benefits, this method eliminates the need to clean an extraneous metering device. A key attribute of the system is its versatility. The unit can perform through-the-tip filling for liquids or viscous products for typical infeed scenarios including hoppers and reservoirs. An optional attachment makes it possible to fill bottles or vials. Suckback control heightens fill accuracy, and all product contact parts are fully disposable.

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Extractable and leachable (E&L) studies have become an integral part of any drug development programme and serve to ensure compatibility between the product and its packaging. While such studies are now generally well defined in terms of experimental design and data evaluation, these have had to adapt to the ever-increasing diversity of therapeutic products. There are, for example, some unique challenges in the analysis of biopharmaceutical products as a result of certain formulation components, as well as the complexity of the therapeutic itself. This article describes a number of challenges and solutions in the E&L evaluation of biopharmaceuticals, and highlights a selection of those encountered with emerging cell and gene therapy (CGT) products.

Ongoing E&L challenges
The risks posed by leachables on product quality and patient safety are an ongoing challenge for the pharmaceutical and biopharmaceutical industries. Continued investigational development in this area is primarily driven by a number of factors, including: the increased adoption of single-use technologies; progress in the medical device field, particularly combinational devices; expanded directives from industry regulators; and advances in analytical technologies.

Extractables (1) are defined as compounds that migrate from any product-contact material (including elastomeric, plastic, glass, stainless steel, or coating components) when exposed to an appropriate solvent, under exaggerated conditions of time and temperature. To study materials at risk of potential leachable components, extractions of the contact material are performed, generally using aggressive conditions including acidic, basic, organic, and aqueous solvents. These conditions are not intended to distort the material under investigation but do attempt to mimic the drug formulation. The resulting extracts are usually analyzed using a combination of analytical techniques such as liquid chromatography–mass spectrometry (LC–MS), gas chromatography–mass spectrometry (GC–MS), and inductively coupled plasma–mass spectrometry (ICP–MS) that can qualitatively and quantitatively evaluate both the organic and inorganic components, or “extractables”. Such studies are typically performed to represent a worst-case scenario and may provide an indication of possible leachable components as well as facilitate material selection during early risk assessment.

Leachables (1) are compounds, often identified during extraction studies, that migrate into a drug formulation from any product-contact material (elastomeric, plastic, glass, stainless steel, or coating components). This leaching happens as a result of direct contact under normal process or accelerated storage conditions, such as elevated temperature. However, if the leachable interacts with the drug product (as may be the case particularly with biotherapeutics) or packaging materials, new components can be generated that are known as “secondary leachables”. The complexity of many formulations, often containing a variety of buffers, surfactants, fillers, and other excipients, can lead to the formation of secondary leachables only identified after long-term stability studies.

Biologic E&L studies: the difficulties
E&L evaluation of traditional pharmaceutical medicines is now well established and may be undertaken with a certain predictability in experimental design and even outcome. In contrast, however, certain excipients used in the formulation of some biotherapeutics present unique analytical challenges for leachable determination. Among these excipients are the commonly used nonionic surfactants, such as polysorbate 80 (Tween 80), which
constitute a mixture of fatty acid esters of polyoxyethylene sorbitan. These have an extremely low ultraviolet (UV) response but are highly responsive to ionization methods commonly used in LC–MS (2). This often leads to significant interference, either by co-elution and/or suppression during analysis, raising the real possibility of contaminants remaining undetected. Extraction of these surfactants prior to analysis is a possible means of mitigation but is often not highly effective due to the surfactant’s inherent heterogeneity and limited extraction efficiency. Care must also be taken in the application of such an approach since the leachable may be co-extracted with the surfactant.

In the growing area of CGT, there are currently no specific guidelines for E&L studies. However, such products have some unique challenges, such as the use of “ancillary materials”. These materials are used during manufacturing but are not intended to be present in the final product. They are often themselves complex biological materials, such as recombinant insulin and human serum albumin, used as media supplements, and collagen, used as a scaffold in implantable devices (3). Since these materials can potentially interact with and be affected by leachables, in the same manner as the biotherapeutic itself, the choice of materials and controls must be carefully considered to avoid adverse consequences for the manufacturing process.

The evaluation of biotherapeutics for leachables presents many challenges, some of which are somewhat unique to this type of product. For example, the biopharmaceutical itself may interfere in the testing regimen due to its high concentration, heterogeneity, and/or high detector response. A potential solution is to remove the biotherapeutic prior to analysis, but the procedure must be very carefully considered because associated leachables may be unknowingly removed and/or additional extraneous components may be introduced.

The major concern of leachables in pharmaceutical products is their specific toxicity and/or genotoxicity. The additional issue with biotherapeutics is the potential for interaction between the structurally complex biopharmaceutical itself and any leachable components. Compared to traditional pharmaceuticals, proteins and other biotherapeutics are often significantly less stable, due to their strong dependence on physico-chemical and conformational structural properties. These larger molecules often have both hydrophilic and hydrophobic regions, with many reactive sites for possible leachable binding, potentially resulting in the loss of activity via mechanisms such as unfolding, truncation, aggregation, and precipitation. Consequently, the adverse effects of extractables and leachables can be more significant and more difficult to assess on biopharmaceutical products than small molecules. Acrylic acid, for example, a leachable from syringes, has been shown to react at three different sites within a protein structure, resulting in potential changes in charge and hydrophobicity with consequential effects on the therapeutic properties of the protein-based drug (4).

As the manufacture of many biotherapeutics involves cellular-based processes, the presence of certain leachable components can have unfavourable consequences not only on the final drug product but also on the production process itself. Productivity can certainly be adversely affected by leachables that result in cellular toxicity, leading to significant loss in manufacturing yield.

During the past decade, many biotherapeutic manufacturers have migrated to the use of disposable, single-use systems (SUS) for production, and this has now become commonplace in the emerging CGT field. Every operational phase of a biomanufacturing process that uses SUS technology is at risk of leachable contamination. This contamination can be introduced as a result of contact and interaction with different materials, such as polymers, metals, and additives used to construct holding tanks, films, bags, tubing, and filters. This concern extends to containers for buffers, media, water for injection, and other liquids required for manufacturing. The possibility of leachable accumulation may also arise since concentration stages are often used in the manufacturing process.

The majority of biopharmaceuticals are injectable products and, therefore, contaminants enter the bloodstream directly, without the potential for depletion in the gut as with oral medications. In addition, many biotherapeutics, particularly monoclonal antibodies, are dosed in high concentrations (multiple mg/mL) and are produced in liquid, with complex formulations. These drugs can be stored for long periods of time, providing higher risk of leachable adulteration of the product than the solid dose forms common with traditional pharmaceuticals.

Certain products developed in the CGT area can present further challenges for E&L evaluation. Since the quantities of product can be relatively low, the ratio of contact material surface to the drug volume is very high, increasing the potential for leachable contamination. This may be further exacerbated in those treatments that are essentially customized, with each patient receiving the entire product dose.

**Product development strategy**

Risk assessment in terms of E&L is now an integral part of any product development strategy. This is of particular importance for CGTs, which should not only evaluate...
the likely compatibility of contact materials used in manufacturing, but also include an experimental study designed to provide an accurate assessment of the extractable and leachable profiles.

**Some biotherapeutic excipients, and the drug itself, may also play a significant role in facilitating the extraction of metals from contact surfaces.**

While many biotherapeutics are produced as liquid formulations, lyophilized forms of drug product are also commonplace, as part of efforts to improve stability during storage. Interestingly, the US Food and Drug Administration (USFDA) Center for Drug Evaluation and Research, the USFDA Center for Biologics Evaluation and Research, and the United States Pharmacopeial Convention (in United States Pharmacopeia <1664>) [5], describe sterile powders for injection as being “low risk” for leaching, despite some evidence to the contrary. It has been demonstrated, for example, that several semi-volatile organic compounds originating from butyl rubber stoppers—part of the primary packaging system—may leach into a lyophilized product but not a liquid formulation stored in the same packaging (6). The explanation for this finding lies in the hydrophobicity of the leachables, rendering them very poorly soluble in aqueous media but able to diffuse from the stopper. This is perhaps facilitated by their volatility and the nature of the drug product.

There are multiple types of material used in the manufacture and storage of biopharmaceuticals, and most may be classified as either glass, metal, or synthetic polymer/elastomer. The latter are recognized as the most significant sources of leachables, often resulting from monomers/oligomers of the polymer itself, as well as catalysts, initiators, additives (e.g., lubricants, antioxidants, antistatic agents), adhesives, anchoring agents, adhesive resins, colours, fillers, and degradation products of almost all these components. The diversity and nature of these potential contaminants and their often-unpredictable interactions with formulated biopharmaceuticals pose significant challenges to analytical assessment of the drug products and process materials. There are now significant guidance documents available from regulatory authorities, industry organizations, and researchers providing at least some support in the design and rationale for suitable experimental approaches.

For biopharmaceuticals, inorganic leachables (generally associated with glass and metal) are of particular concern because of their potential impact on the stability and efficacy of the drug itself. A metal commonly used is stainless steel, which has found applications in manufacturing, shipping, and storage. Stainless steel is also known to leach iron, chromium, and nickel, particularly if the steel is unpассивated (7). Trace levels of metal ions can potentially cause protein degradation by mechanisms such as protein oxidation and fragmentation. The latter occurs because of the metal-binding propensity of aromatic amino acids such as tryptophan, tyrosine, and histidine. Certain proteins—protein binding is also known to induce secondary and tertiary structure changes resulting in the formation of insoluble protein aggregates (8).

Glass has also been demonstrated to be a source of certain metal leachables. For example, manganese and iron oxides—used as colouring agents—are present in Type I amber vials as are zinc and barium oxides. Higher levels of manganese and iron have been shown to leach from amber glass compared to clear glass. Meanwhile, sterilization techniques, such as steam autoclaving and gamma irradiation, may also lead to the presence of metal ion contamination (9).

Some biotherapeutic excipients, and the drug itself, may also play a significant role in facilitating the extraction of metals from contact surfaces. Certain proteins and chelating agents, such as ethylenediaminetetraacetic acid, have been shown to increase the quantity of metals such as aluminum, calcium, and iron from plastic container systems. Similarly, buffers such as phosphate and lactate can also increase the metal leaching from both metal and glass surfaces.

**Inorganic leachables are of particular concern because of their potential impact.**

The area of E&L investigation has developed rapidly over the past decade, resulting in technological and regulatory advancement. Ultimately, this has led to safer medications. However, developments in biopharmaceuticals and specifically in CGT are likely to present further demands on expertise in areas of manufacturing and analytics.

It is clear that a single, common strategy, for monitoring and/or eliminating leachable contaminants will never be sufficient to address all situations. Instead, engineers and investigators must be always prepared for the unexpected.

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Survey of QPs on Remote Certification

Despite some improved understanding of adapted processes in light of the pandemic, information is still not filtered throughout the qualified persons community fully and more work by authorities and associations is required to improve communications.

Dr. Ulrich Kissel is chair of board of the European QP Association; with editorial input from David Cockburn, board member of the European QP Association.

In view of the COVID-19 pandemic and work-from-home guidance from public health bodies, the European Qualified Persons Association (EQPA), in March 2020, surveyed its members on the topic of “Remote QP Certification” (i.e., batch certification performed by a qualified person [QP] whilst not physically present at the site of the manufacturer). The topic was perceived as an area of non-harmonized national interpretations, and EQPA sought to better understand the differences across the European Union/European Economic Area (EU/EEA) and on how QPs positioned themselves in such a procedure.

One year later, in March 2021 with the pandemic still ongoing, it was expected that the situation in all organizations would have now settled with new modes of operation, including the QP certification procedure. EQPA decided that in the interests of all QPs it was time for a review on how this difficult period is being managed today. More than 300 QPs responded to a follow-up survey in which similar questions to the original survey were posed.

The shift in the pattern of answers is, for the most part, quite modest although significant in some cases. It reinforces what was seen in March 2020 but with greater use of remote certification and more developed procedures generally. That may not necessarily be true with respect to the personal experience of each individual QP.

EQPA was interested in whether rules on remote certification might change in view of the pandemic and whether national legislative changes have been made that would continue beyond the pandemic period. As far as most QPs are aware, national rules on the topic, whether pre-existing or non-existent, have changed, but only for the duration of the pandemic. In March 2020, 50% of QPs across Europe believed that on-site certification was mandatory in their country. During the pandemic, this changed dramatically, and now 81% of QPs confirm that remote certification is allowed. This change is almost certainly because of the joint notice to stakeholders published, after the first survey, by the European Commission, the European Medicines Agency (EMA), and Heads of European Medicines Agencies in April 2020 indicating that all member states would accept remote certification in the light of the pandemic (1). This notice followed confirmation, in February 2020, by the Medicines and Healthcare products Regulatory Agency (MHRA) via its inspectorate blog that there was no legal obstacle to remote certification in United Kingdom (2).

It appears, in the case of countries where on-site certification was previously mandatory, that this change to remote certification is temporary as no legislative changes are known to have been made.

The survey outcome becomes even more interesting if we sort the responses by country (Figure 1). A significant shift towards awareness of the acceptance of remote certification in most countries is apparent, reflecting the aforementioned official notice to stakeholders, but oddly, Italy and Romania show the opposite trend. Although the question, as posed, essentially required a “yes” or “no” answer as to whether the law allows or does not allow remote certification, the mix of answers from respondents from nearly each country demonstrates continued lack of clarity on this topic. After a whole year of the pandemic, neither QPs, nor the authorities, nor EQPA can provide clear and conclusive information to settle this question. Consequently, EQPA will continue to focus on this topic and will seek a harmonized regulatory approach across the whole of the EU/EEA.

It is surprising that despite the pandemic and official communications we do not see a uniform shift towards the right (awareness of the acceptance of remote certification) in the Figure 1. The survey question actually offered three responses to choose from: not allowed, allowed but I do not use it, and allowed and I use it. Table I shows this three-way split.

Across Europe in March 2020, nearly 20% of respondents did not believe that remote certification was accepted
even in the midst of a pandemic. It is assumed that the difference in the more recent survey results can be attributed to the notice to stakeholders of March 2020. It is disappointing to note that the channels used by the health authorities and those of EQPA failed to reach all QPs effectively. In contrast, for example, the EQPA has seen a copy of a message understood to have been sent by the Irish Health Products Regulatory Authority (HPRA) to all QPs in Ireland, informing them of a relief from the obligation to perform certification on-site and the circumstances to be met to take advantage of this. Not surprisingly, as seen in Figure 1, such direct mailing was very effective, although still not 100%.

That said, QPs need to always be aware of national implementation or interpretation of European rules. EU directives are transposed to national law to fit with national circumstances and national authorities often add specific requirements resulting in some intra-EU variability. This is part of the EU system and works in practice, provided the objectives of the directives are met and that added national requirements do not interfere with the operation of the single market. For remote certification, we have the situation that an official communication by EMA and the heads of all of the national medicines agencies intending to waive national rules, at least for the duration of the pandemic, but national differences persist in practice. EQPA will continue to take a position against unnecessary national differences on this matter and call for a harmonized approach to remain after the pandemic is over. It has also been noted that differences can even exist within an individual member state so that one QP performing remote QP certification is supported by the authorities whereas another QP is not.

Despite the notice waiving any national requirements that restrict the ability to certify remotely, still 20% (2020: 23%) of QPs do not believe that, even in the midst of the COVID-19 pandemic, remote certification is a legally defensible option to pursue. From those who are aware that the option is possible, less than half of them used it in March 2021. In total, approximately 65% of QPs continue to perform certification on-site only.

Remote QP certification may need more regulatory specification given that it is not yet a properly
defined concept. Whereas, it is clear that QPs can only be listed in EU manufacturing authorizations, giving clear territorial limitation to such activities, and importation testing can only be executed on EU soil, the definition of certification given in Annex 16 omits any similar territorial link or restriction. Let us imagine a scenario where a QP is employed in Germany but is domiciled in Switzerland. This is a possible scenario but not for QPs for pharmacovigilance (QPPVs) according to directive 2001/83/EC (3). In view of the pandemic, if the aforementioned QP decides to work from home, is it now legally acceptable to certify remotely from a third country? The Mutual Recognition Agreement (MRA) with Switzerland, like all similar MRAs, is built on the concept that QPs cannot be established in Switzerland. For certification to be accepted by the EU, it has to take place within the EU. A potential conflict now emerges.

One of the survey questions explored which arrangements were seen as most important by QPs for establishing and maintaining remote certification. Some shifts can be seen in the most recent answers compared to the first survey. More importance is given to having clarity on the location where certification takes place (63% → 74%) and assurance that a complete set of documents and data is available (84% → 91%). Reduced interest is noted on clarification of the location of the batch register (76% → 56%) and oversight of the quality system (78% → 71%). This may nevertheless be more indicative of the greater challenges posed here by the pandemic rather than a conscious shift in bias. Twenty percent of respondents in 2021 (30% in 2020) are satisfied with limited data and documentation to support remote certification during the pandemic. This poses a critical question as to why a certification procedure conducted remotely would need to be supported by different batch data and documentation compared to on-site certification.

One issue that needs to be resolved when using remote certification is the appropriate exchange of data, documents, and certificates. In good manufacturing practice (GMP) environments, this can occur either by paper or validated IT systems. Email should not be considered robust or compliant, and it may not be amenable to validation according to Annex 11. Up to 80% of QPs in the follow-up survey are able to rely on direct access to IT systems, exchange platforms, paper exchange, or hybrid systems. This is a slight increase of 5% compared to March 2020. Still, between 16 and 20% of existing procedures rely mainly, or fully, on emails. Those procedures should be highlighted for urgent change if they have not already been identified as a GMP deviation. Exchange platforms supporting remote interaction are available that provide safe data, documentation, and certification exchange.

A series of the survey questions explored how remote certification was introduced in terms of the Pharmaceutical Quality System (PQS). Roughly one third of the responses indicate that a deviation was opened, half of the responses confirm a change request and 75% finally adopted procedures within their PQS to better describe the remote certification procedure. Annex 16 and other references require many tasks to be completed prior to certification of a batch. One of the survey questions explored a potential list of data, evidence, and documents that the QP should have to hand to support remote certification (Figure 2). From March 2020 to March 2021, QPs significantly improved their access to relevant data, evidence, and documents to bolster their remote certification procedures, which is an encouraging development. While in March 2020,

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Figure 2: Data elements available to the qualified person (QP) during remote certification. QC is quality control, OOS is out of specification, PQR is product quality review, and MA is marketing authorization.
Considering Annex 1
Revisions: Expert Insights

The draft revisions of Annex 1 are driven by a quality risk management approach and will provide more clarity and detail for manufacturers.

Felicity Thomas

The European Union’s good manufacturing practice (GMP) guide for sterile products, Annex 1, has been under review for some time, with the revisions being considered more along the lines of a rewrite due to the extensive and comprehensive nature of the changes. In a webinar, hosted by the Parenteral Drug Association (PDA) Ireland Chapter, experts outlined key changes, considerations, interpretations, and ways of implementing the revised guidelines. In this article, some of the fundamental insights from that meeting are summarized.

Driven by quality risk management

Pre-use, post-sterilization integrity testing (PUPSIT) is not a new requirement, explained Andrew Hopkins, director operation quality, Quality Assurance Audit and Compliance, AbbVie, ex-Medicines and Healthcare products Regulatory Agency (MHRA) regulator, and previous member of the Annex 1 working group. As there was no clear push from regulators or industry on the matter of PUPSIT previously, there is the misconception that it is a new addition brought in with the latest revisions; however, it has been included in the Annex 1 guidance since 1997, he revealed in the webinar.

PUPSIT specifically pertains to the integrity testing of the sterilizing filter and assembly. The reasoning behind why it is necessary is because filters can become “blind” and can mask flaws during post-use integrity testing, which would have an impact on the quality of a product. Work on the mechanisms and risks of filter flaw masking is being performed by PDA and the Biophorum Operations Group (BPOG); the results are not yet completed or published at the time of writing, but there has been some evidence of masking, which means it is an issue to be wary of, warned Hopkins.

In the latest revisions of Annex 1, however, the wording for PUPSIT is much more driven by quality risk management (QRM), which means that satellite navigation risk assessments cannot be used when risk assessments are performed. It is important to be completely honest about them and base them on scientific justification, emphasized Hopkins.

The contamination control strategy (CCS) is also based on QRM principles, with an emphasis on good design for equipment, facility, and processes in the first instance, then on well thought out procedures, and finally on the monitoring system, Hopkins stated. The last sentence in the revised document, which says, “exclusively monitoring or testing does not assure sterility,” was highlighted as being of particular import by Hopkins.

Another aspect of the draft Annex 1 revision, that caught the attention of Hopkins, is the fact that there is discussion around how a CCS is a number of aspects that are put together rather than individual items, which would not achieve the required item in isolation. “So, it’s how all of those individual items work together to give you the overall CCS,” Hopkins added.

Furthermore, the revised guidance emphasizes the need for the correct people to develop the CCS (i.e., those people with the necessary technical and process knowledge). “I think that [aspect] is really important,” added Hopkins. “[The CCS] is not something that is developed by either the quality assurance (QA) manager, sat in his office, or the production manager, or one person, it is about making sure that all of the right people are involved.”

“The other key thing to realize,” Hopkins continued, “is that [the CCS] is supposed to be a dynamic process, and [the revised draft] talks to periodic reviews.” Based on his experience as a regulator, Hopkins’ opinion is that a periodic review tends to indicate an annual occurrence, at least.

Currently, the Annex 1 that is in place is “silent on the CCS” revealed...
Hopkins. However, this does not necessarily indicate that it is a new requirement, and, in fact, there was some talk of contamination control in the Chapter 3 GMP requirements that were brought into operation in 2015 (4), he added.

QRM principles, which are also discussed in the International Council for Harmonisation Q9 guideline (5), are important to bear in mind when approaching a CCS, asserted Hopkins. These principles are focused on scientific knowledge and protecting the patient, but also, are steering the industry to the fact that the level of effort put into the evaluation of risk to quality should be commensurate with the risk.

“So, with steriles, we’re going to be tending toward that higher end of the risk element, but there may be bits that aren’t quite as important as other bits, so make sure you put the right work in at the right stage,” Hopkins confirmed.

The CCS needs to be a living document that is reviewed periodically, taking into consideration various feedback on processes, information on monitoring, or technological improvements that need to be included, and so on, to ensure that the strategy continues to work, Hopkins stressed. Importantly, the document should be written in a way that it is understandable to an inspector, and widening that out, it should be simple enough for everyone to understand, he summarized.

Aseptic process simulations
Despite there not being much change in terms of the Annex 1 revision and the requirements of aseptic process simulations (APS) for manufacturers, there is certainly now a lot more detail included in the guidance, revealed Greg McGurk, executive director Industrial Operations and Product Supply, Regeneron Pharmaceuticals, ex-Health Products Regulatory Agency (HPRA) regulator, and previous member of Annex 1 working group.

An aspect of the thought processes behind APS in the revised guidance is whether or not they are a true aseptic validation strategy or if they are an evaluation of the process and ongoing process controls, which led to the topic being moved in the guidance to the section where process monitoring is discussed, McGurk explained in the webinar. “When you consider [APS], they do form part of the overall CCS, so to speak, in that they are used to monitor those controls and minimize the risks associated with aseptic processes,” he said.

General aspects of the requirements laid out in the draft revision document are that manufacturers must represent the worst-case operating parameters in APS, which is nothing new, but the revision incorporates an element allowing for the use of surrogate materials, McGurk specified.

“Typically, we haven’t seen the allowance of surrogate materials over the years,” he noted. “APS is a science-based approach, however, and so whatever material you are using should not inhibit growth and should not impact the capabilities to recover growth or contamination. So, if a surrogate material is used, it has to be based in good science.”

Processes should be imitated as closely as possible, with a requirement for all aseptic operations, manipulations, and interventions that routinely—and, in some cases, non-routinely—would occur, to be evaluated, McGurk stressed. “One aspect that has been incorporated into the revision is a section on more complex unit operations,” he said. The intent of the section was in relation to an attempt to achieve a continuous evaluation of processes from one unit to another. The guidance in the draft states that this should be avoided where possible, but under certain circumstances it can be justifiable, McGurk added.

Lyophilization evaluation expectations are more detailed in the revised guidance, McGurk highlighted. The loading, unloading, and chamber dwell time information are required, and manufacturers are required to replicate the maximum time between sterilization and lyophilization, as well as the maximum hold times post-sterilization and lyophilization, he explained. All those aspects need to be incorporated into the overarching strategy, in addition to the largest number of trays that will need to be lowered into the lyophilizer, the longest duration of loading, the length of time the chamber may be open, and so on. “I think it is good that the draft does provide an additional degree of clarity around those expectations,” McGurk stated.

Additionally, the draft Annex 1 provides some definition around inherent and corrective interventions, McGurk continued.

It is important to incorporate these interventions into the APS so they can be evaluated and addressed appropriately, but when designing or selecting the types of interventions to include, it is critical that the choice is not justified based on the facility design or process design, McGurk emphasized. “[Justification via facility/process design] is just not based on good science, it is not based on minimizing risk necessarily,” he said.

The draft Annex 1 provides some additional guidance on how to develop the APS strategy overall and includes the expectations of elements that must be considered in the strategy. “So, obviously it is necessary to identify and assess the worst-case container size, line speed, container closer, or all of those, and you have to look at all the variables,” McGurk specified.

“If a bracket or matrix approach is being taken, then you should justify the choice of variables that are being incorporated into the overarching APS strategy.”
Volume and agitation are other considerations in the APS strategy. It is therefore important to ensure whatever volume is being used can contact all the equipment in component surface, and if agitation and/or inversion may be required to ensure full exposure to surfaces is achieved, McGurk explained. A consideration has also been incorporated into the revised draft of Annex 1 for anaerobic simulation, he added.

The revised guidance thus provides more clarity on APS, and it is dependent upon the application of QRM to evaluate what is necessary to ensure a robust assessment of the process is being performed, McGurk confirmed. Furthermore, there is mention of manual filling, which is high risk and should be avoided where possible, McGurk added. Again, the revised draft provides guidance and clarity on the expectations for such processes that are high risk.

Moreover, it should be noted that the target for APS is to have zero growth, so any contaminated unit will result in a failed process simulation, McGurk stressed.

“There were some caveats in the Annex 1 previously, which allowed for a degree of failure,” he said. “However, when dealing with APS, it is imperative to understand what the failures are and to investigate the root causes of the failures.”

In determining the root cause of a failure, if a corrective and preventive action that impacts the APS is identified, then this will call into question every batch since the last successful simulation, and it may be necessary to perform the three consecutive runs again until success is achieved, McGurk stated. “So, there are multiple elements to incorporate within such investigations, and QRM is very much one of the key fundamental elements incorporated into the draft,” he summarized.

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for example, process validation summaries were only available to 50% of QPs. A year later, these summaries are available to 58% of QPs. Despite this improvement, validation summaries stay the weakest area of the offered list of data elements; whereas, the range of confirmed availability is now between 58–100% (2020: 50–96%). Note that the potential list of data elements used in this survey question for respondents to select from was taken from the MHRA Inspectorate blog published in February 2020 in which MHRA expected all to be available to QPs (2).

The importance and meaning of the batch register remains a continued area of discussion within the QP community. Its importance seems to have diminished considerably judging by the shift in the answers between the two surveys. While in March 2020 at least 76% of respondents agreed that it was important to clarify the location and control of the batch register in the context of remote certification, in March 2021 this was considered important for only 54% of QPs. This seems to indicate that the register is disregarded by many QPs, whether for good and bad reasons. The authors nevertheless continue to point to the definition of QP certification according to Annex 16. According to this, certification cannot be completed or executed without a register or equivalent; although notably, it can be completed without the issuance of a batch certificate. Either the requirement needs to be clarified to better understand the purpose of the register, or it may even be eliminated. Better training of QPs on this aspect may be needed.

Summary and conclusion

Repeating the survey for a second time was intended to show progress in arrangements around Remote QP Certification and how QPs coped throughout the pandemic. While many QPs made obvious progress to stabilize their certification processes in light of the pandemic, some gaps remain and should be closed. Data exchange could still be improved for many, and some gaps and hurdles remain in relation to access to a regular set of data to support remote certification. While gaps may be found in execution of remote certification, shortcomings also exist in harmonized rules for its execution as well as on related matters, such as the role and use of the batch register and data elements needed to support certification. Although health authorities and associations like EQPA made information and new aligned positions publicly available, there is still room for more efficient and effective communication in a rapidly changing scenario. One of EQPA’s aims is to ensure that QPs do not miss new applicable guidance, or its interpretation, on topics crucial to continued operations. It is not acceptable that QPs should be unaware of public guidance one year after its publication.

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Balancing Pressing Priorities

CMOs and CDMOs adjust business processes as demand for COVID-19 treatments and non-pandemic related therapies puts pressure on the bio/pharma industry.

Susan Haigney

After more than one year of rapid development and production of vaccines and therapies to address the COVID-19 pandemic, the bio/pharmaceutical industry is adjusting business practices and priorities as the next phase of response to this global emergency unfolds. Bio/pharmaceutical contract manufacturing organizations (CMOs) and contract development manufacturing organizations (CDMOs) are adjusting to a variety of demands and challenges caused by the pandemic, including ensuring a robust and safe supply chain. When the pandemic initially began, many companies had to not only prepare for the influx of demand for COVID-19 treatments, but they also had to balance that demand with their existing workload. The CMO/CDMO industry was operating on a reactionary basis during the beginning of the pandemic, according to Tom Wilson, contract manufacturing lead at Pfizer CentreOne. “As it became apparent that we would be in this state for the long-term, we had to change our business processes and develop best practices to ensure we could partner remotely,” he says. Collaboration increased across CDMOs, says Wilson, and requirements were prioritized to meet the needs of patients.

Reevaluating the supply chain and timelines

The pandemic highlighted a variety of issues related to the biopharmaceutical supply chain, and supply chain risk mitigation, especially for APIs, has become increasingly important, says Gene Nakagawa, EVP business development at LGM Pharma. “In 2020, we saw an increasing focus on outsourcing of products directly related to COVID-19, such as Midazolam for intubation, antivirals, etc. Drug shortage lists have also been growing, partially due to demand but more often due to supply chain issues. In particular, starting materials for APIs have been hit with shortages,” Nakagawa says. “Supply chain has been difficult for many companies and continues to be. This has heightened the importance on safety stock and applies to both excipients and APIs.”

Joe Sinclair, vice president, corporate strategy and business development at Vibalogics, agrees the pandemic caused a global trade disruption, and supply chain management is crucial. “For many, this has meant evaluating alternative sources of raw materials, consumables, and suppliers for contract manufacture and product quality control testing,” Sinclair says. “Companies are actively focusing on mitigating risks by evaluating the expansion of their network of suppliers, and often onshoring activities or searching for domestic sources due to supply complexity, and the risks of being reliant on a single supplier, or a single region.” Vibalogics has optimized the security of its own supply networks and expanded its operations in the United States and Europe to address supply chain concerns, according to Sinclair.

The expectation of accelerated timelines also is a significant impact of the COVID-19 pandemic on the bio/pharmaceutical outsourcing industry, according to Mike Kleppinger, chief commercial officer at AMRI. “There has been a compression over the past 18 months that demonstrates the ‘art-of-the-possible’ in a crisis. We didn’t have the luxury of months-long contractual obligation discussions. COVID brought about a common purpose that drove more efficient timelines and was very outcomes-driven,” Kleppinger says.

“When it comes to clinical trials, market demand is high for products being manufactured by CDMOs. It’s a critical juncture where capacity is being challenged as trials that were delayed last year by COVID are now starting back up just as new trials are commencing with products that were in the preclinical phase a year or so ago. Those combined have accelerated demand for product,” says Bill Vincent, chairman and CEO at Genezen. In addition, approval requests for COVID-19 vaccines have increased the wait time for approvals for clinical trials for gene therapies, agrees Geraldine Guerin-
Peyrou, director of Marketing and Communications at Polyplus. “Add to this the continued trend of new, and often well-funded, start-up companies entering the cell and gene therapy space and there are even more products coming for limited capacity in the CDMO industry,” Vincent says. In addition, he says, demand has been compounded by the limited supply of raw materials and disposables caused by the need to produce COVID-19 vaccines. “It is likely that manufacturing capacity and supply of raw materials will be constrained for at least another year, but CDMOs (including Genezen) are investing in new facilities to address this,” Vincent says.

Changing demands for APIs

The surge in demand for specific APIs to treat COVID-19 patients, or investigate the use of existing drugs as treatments, in some cases impacted availability.

Wavelength Pharma, an API custom developer and manufacturer, saw an increase in demand during the pandemic due to the need for drugs to treat respiratory conditions in patients on ventilators for lengthy periods. “This sudden requirement to significantly boost production has emphasized the importance of adaptability for API CMO/CDMOs to maintain an uninterrupted drug supply, with some organizations proving better able than others to handle the pressures of rapid scale up to respond to the surging global demand,” says Ilan Avni, VP business development, marketing and IP, Wavelength Pharma.

“When it comes to new developments, a few bio/pharma companies are developing, or repurposing, molecules for COVID patients, and we are in discussions with a number of key players in the field. We have seen a number of innovators rejig their portfolio—speeding up drugs with a focus on COVID-19 while slowing down some of the other developments. We have seen an increase in outsourcing and have benefitted from the trend even as we continue to invest in capacity to meet customer needs,” says Saharsh Davuluri, vice chairman and managing director at Neuland Labs.

Going virtual

The pandemic also impacted the way the industry conducts business, says Britton Jimenez, vice president, business development at Metrics Contract Services. Virtual audits and site tours are now more common, as well as virtual internal and external meetings. “Many of these new practices that have been implemented will remain, but I do see the face-to-face engagement returning back to pre-pandemic state,” Jimenez believes. “Video conferencing and remote communications dominate the way we perform internal and external communications. Since there is no way to visit facilities for an audit, at least in India for the time being, CMOs who have good track record will continue to get recommendations from fellow clients,” says Davuluri. Utilizing virtual technology has alleviated disruption and created more time for important tasks, according to Davuluri, but it also highlighted the importance of face-to-face interaction.

The industry as a whole has also continued to learn and connect virtually. “The virtual international conferences have also allowed for scientists that usually don’t travel to participate and to hear about the latest innovations, hence we may see a rush of scientific outbreaks in the next few months due to this,” states Guerin-Peyrou.

New parameters created by the pandemic caused business challenges for some companies, and attracting new clients became difficult. “Without the traditional methods of in-person meetings and audits, sponsors have adopted and accepted the need to use virtual methods of communication and remote technologies to access and assess potential partners,” says Andrew Henderson, chief commercial officer at Sterling Pharma Solutions.

Adapting and adopting new practices

To adjust to these challenges, companies have taken stock of their processes and strategies. “COVID-19 has made everyone in the industry revisit their sourcing strategies and risk management; even companies with stable in-house facilities have reassessed their risk profiles and vulnerabilities in supply chain, and sought after CDMO partnerships,” says James Choi, chief information and marketing officer at Samsung Biologics.

Choi sees the company’s investments as important to enduring the trials of the pandemic. “For example, our investment into Plant 4 expansion, the opening of our San Francisco R&D Center, and providing mRNA vaccine fill and finish, are few of our preemptive approaches in response to the shifting industry,” he states. “Our sustainable and robust business management systems, in which we have invested proactively to be ISO 22301-certified across all of our business areas, have been central to withstanding market disruptions over the last 18 months amid the COVID-19 pandemic.”

“For Vectura, there have been two areas of focus: keeping our people safe, and minimizing disruption to the supply of medicines and to our customers,” says Matthew Barker, director, Corporate Strategy at Vectura.

“Our team has embraced new ways of working, which include adhering to new health and safety protocols across sites; showcasing our inhalation expertise virtually at conferences; and navigating the sales and supplier audit processes remotely.”

Adapting became key to meeting demand. “We embraced technology, looking for new ways we could communicate effectively and developed innovative audit processes which enabled us to meet obligations,” says Wilson.

Balancing demands

In 2020 and 2021, CMOs and CDMOs found themselves needing to balance the demand of the development and manufacture of treatments of COVID-19 with the projects in the pipeline and new non-COVID-related products.
Some companies expanded capacity and resources to meet these priorities. While noncritical therapies were de-emphasized for a few months because of COVID-19, according to Kleppinger, manufacturing these products was still necessary during the pandemic. “We didn’t experience a disruption in our traditional business demand because of COVID; what we found was COVID was additive to our workload,” he says.

“CDMOs, such as Vibalogics, have taken steps to expand their capacity, and to use their existing resources to adapt their business to not only the vaccine service market, but also to build strength in capability for the classes of next-generation modalities,” says Sinclair.

“CDMOs are waiting for consensus on vaccination guidelines, especially multi-year demand for COVID-19 vaccination, to address lingering supply challenges for first-round vaccinations, while building further strength into ongoing supply demands. There are still many companies optimizing their approach, initiating Phase I clinical trials, and looking to bring further benefit to market by building supply security with additional approved and technologically advanced modalities,” says Sinclair.

“Away from the now-established supply chain of COVID products, there remains the need to support innovation and research in the existing development pipelines as pharma companies concentrate on their core indications,” says Henderson. “This remains as strong as ever, so the need for CDMOs to be flexible and to be able to support these is crucial. This does not mean that there is a shift in focus, but companies need to have the capabilities to support the evolving needs of innovators.”

Oncology’s place at the top of the contract manufacturing industry’s focus was shifted to treatments for infectious diseases, says Vincent, citing market research data (1). Because COVID-19 vaccines are now getting approved, the shift in focus has turned back to non-COVID products. “The immuno-oncology market particularly is expected to continue growing and witness minimal impact from the COVID-19 pandemic, with 2020 accounting for a momentary decline (2). Given the complexity of products and the prevalence of small biotechs involved in the market without the necessary infrastructure to scale and manufacture products, reliance on CDMO partners will be a key requirement for the foreseeable future,” Vincent says.

“A lot of potential opportunities for CDMO services are focused on ANDA/OTC [abbreviated new drug application/over-the-counter] products not related to COVID-19. There is also an anticipation that cough/cold will come back as the economy starts to open up and kids are back in school,” says LGM Pharma’s Nakagawa.

“Non-COVID products are back in demand, but timelines have shifted,” says Guerin-Peyrou. “For gene therapy, delays to get GMP AAV manufacturing slot can be from 12 to 18 months today.”

While the demand for COVID-19 treatments will continue for a while, according to Wilson, most CMOs/CDMOs “are now re-establishing their operating levels and delivering on all obligations.”

Trends in the industry

COVID-19 hasn’t been the only thing to change and shape the bio/pharma outsourcing industry in recent years. Phil Vanek, CTO at Gamma Biosciences has seen some interesting developments in the cell and gene therapy field. “We’ve seen a number of trends that are very interesting in particular within the cell and gene therapy space. The first is the continuing consolidation of a number of the CDMOs that is reshaping the manufacturing landscape—MaTherCell and Paragon acquired by Catalent, Brammer Bio being acquired by Thermo Fisher Scientific, and the interesting move of Charles River Laboratories acquiring Cognate (which in turn had recently acquired Cobra) thereby doubling down on their cell banking and supply services,” says Vanek.

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Company description
Backed by over 85 years of experience in parenterals, Baxter’s BioPharma Solutions (BPS) business collaborates with pharmaceutical companies to support commercialization objectives for their molecules. BPS is a premier CMO with a focus on specialized sterile injectable manufacturing designed to meet complex and traditional sterile challenges.

Primary locations:
- The Bloomington, Indiana facility is a leader in sterile contract manufacturing and offers form/fill/finish services and solutions for injectables designed to meet complex and traditional sterile manufacturing challenges.
- The Halle/Westfalen, Germany facility has over 60 years of experience and is recognized as a world-class manufacturer of oncology products and other sophisticated compounds.

Products/services
BPS can support your pharmaceutical needs with a broad portfolio of sterile fill/finish production capabilities, and our reputation is built on the high-quality products we manufacture for our clients in a cGMP environment. Our delivery systems include: pre-filled syringes, liquid/lyophilized vials, diluents for reconstitution, cartridges, powder-filled vials, and sterile crystalization. Our drug categories include: small molecules, biologics, vaccines, cytotoxics, highly potent compounds, and ADCs (antibody-drug conjugates). From formulation and development, through commercial launch, our extensive, customized support services can guide you through marketplace complexities, helping you achieve the full potential for your drug molecule. Whether you face formulation challenges, clinical supply hurdles, surges in demand due to market fluctuations, risk mitigation concerns, or patent expiry challenges, we offer tailored and versatile solutions to help achieve your commercialization objectives.

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Catalent is the leading global provider of advanced delivery technologies, development, and manufacturing solutions for drugs, biologics, cell and gene therapies, and consumer health products. With over 85 years’ industry experience, 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 clinical and commercial supply.

Catalent employs around 15,000 people, including approximately 2400 scientists and technicians. The company supplies over 73 billion doses of more than 7000 products annually.

**Markets served**
Catalent’s global network of facilities works across all areas of pharmaceutical development, including small molecules, biologics, and advanced therapeutics such as cell and gene therapies.

**Major products/services**
Catalent Biologics is a global leader in development, manufacturing and analytical services for new biological entities, biosimilars, sterile injectables, and antibody-drug conjugates. To date, its proprietary GPEx® cell line development technology has produced 13 commercially approved biopharmaceutical drugs.

Catalent Cell & Gene Therapy is an experienced and innovative partner for emerging modalities, including autologous, allogeneic and viral vector-based therapies. Dedicated sites in Europe and North America provide clinical and commercial manufacturing facilities, including plasmid DNA, and fill/finish capabilities.

Catalent has a wide range of innovative oral drug delivery technologies, and offers partners comprehensive solutions in development, dose design and manufacturing. Its phase-appropriate technologies and expertise include proven bioavailability enhancement solutions and advanced drug delivery technologies, such as RP Scherer® softgel technology, Zydis® orally disintegrating tablets, modified-release capsules, and FlexDose™ stick packs.

Catalent Inhalation has more than 30 years of experience in supporting the development of inhaled products, has full commercial-scale manufacturing capabilities for dry powder inhalers, metered dose inhalers and unit- or bi-dose nasal sprays, and offers complete end-to-end solutions for inhalation dose forms.

Catalent Clinical Supply offers a full range of services for supplying global clinical trials, including supply management, comprehensive packaging solutions, comparator sourcing, cold chain storage and global distribution, as well as specialised supply chain services including FlexDirect® direct-to-patient supply and FastChain® demand-led supply.

**Facilities**
Catalent is headquartered in Somerset, New Jersey, and has a global network of over 45 facilities, including centres of excellence dedicated to early-stage development, cell and gene therapy development, manufacturing and clinical supply.

**Company description**
Catalent is the leading global provider of advanced delivery technologies, development, and manufacturing solutions for drugs, biologics, cell and gene therapies, and consumer health products. With over 85 years’ industry experience, 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 clinical and commercial supply.

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Recipharm is a leading contract development and manufacturing organisation. We offer support for various dosage forms from early phase pharmaceutical development through to commercial manufacturing, including production of clinical trial material and APIs.

Together with Bespak by Recipharm, which specialises in inhaler, nasal technologies and auto-injectors as well as design, development and manufacturing of high-quality drug delivery devices, we provide our customers with fully integrated support for the development and manufacture of inhalation products. Our Recipharm Inhalation Solutions offering spans the whole product lifecycle for these combination products and includes support services such as regulatory strategies and life cycle management to help ensure our customers’ success.

As a top 5 CDMO with extensive experience in inhalation drug product, device design & development and manufacturing, we understand your challenges and can offer you flexible support when you need it. Our expert teams and depth of knowledge means we can overcome the challenges associated with inhalation drug products and devices and support you every step of the way.

By developing inhalation products with the device and commercial manufacture in mind we eliminate hurdles, mitigate risk and reduce your time to market. One partner, one solution to take you seamlessly from development to market.

Markets served
Whether you’re a big pharma company outsourcing a key stage of your production or a small to medium sized specialty firm seeking support in the development, transfer and production of a product, we’re a reliable option.

By helping to manage the complexity of processes and projects, we reduce the risk for our clients.

Major products/services
We offer expert solutions from pharmaceutical development to commercial manufacturing services across a wide range of dosage forms. Our integrated inhalation solutions offering with Bespak by Recipharm means we can take your inhalation drug products and devices from concept through to commercial.

We specialise in drug delivery devices and have the skills and expertise to continue to develop new technologies to meet our customer’s needs.

Facilities
Recipharm is a global CDMO with a HQ in Stockholm, Sweden. Our company unites over 30 facilities across 10 different countries:
- France
- Germany
- India
- Israel
- Italy
- Portugal
- Spain
- Sweden
- UK
- USA

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Shimadzu

Company description
Shimadzu is one of the worldwide leading manufacturers of analytical instrumentation, since more than 50 years active in Europe. European headquarter is 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 flavours 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
AOC-30 Series: Extending the need for next-generation laboratories
The new AOC-30 series of automatic sample injection systems for gas chromatographs is equipped with unique technologies and functionalities. The systems offer the automation, productivity and remote operability needed for next-generation laboratories. The new series helps ensure that anyone can operate the instrument and obtain expert-level results for routine analysis work in pharmaceutical, chemical and environmental fields. “Analytical intelligence” functionality relieves operators from organizational, input and processing tasks.

Figure 1. Despite a compact size that fits within the GC unit footprint, the AOC-30 series enables automatic analysis of 30 samples to support a wide variety of routine analyses.

TOC-1000e: On-line TOC analyzer designed for pure water applications
Shimadzu’s TOC-1000e is the first analyzer in the eTOC series of on-line TOC analyzers designed for pure water applications. The pioneering TOC-1000e system has the world’s smallest and lightest cabinet and provides high-sensitivity detection, making it ideal for fields requiring high-purity water applications, such as precision manufacturing, pharmaceuticals, and semiconductors.

Figure 2. With its small footprint of less than A4 size, the TOC-1000e can be installed flexibly—either as table-top, wall-mounted or pole-mounted.

Facilities
Shimadzu operates production facilities and distribution centres in 74 countries. In the European headquarter 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, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, France, Germany, Italy, Macedonia, Norway, The Netherlands, Romania, Serbia, Slovakia, Sweden, Switzerland, and the United Kingdom.

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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.

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Q. We are a US-based start-up company, and we are about to put our quality management system in place. One of our consultants advised us to review Form 483 and warning letters issued by the US Food and Drug Administration (FDA). We looked at some of them but are unsure what we are expected to find or what to do with the information in these documents. Do you have any advice?

A. At the end of an FDA inspection, the inspectors will document observations of deviations from the codified regulations on Form FDA 483 (1). This document contains only the inspector’s most significant observations. Other observations may be communicated to the company verbally during the inspection. Importantly, FDA does not classify its inspection findings (e.g., as critical, major, or minor).

The inspector(s) submits his or her report to a district office. The district office classifies an inspection in one of three ways:

- **Official action indicated (OAI),** which means that the inspection was unsatisfactory, and the district advises enforcement actions.
- **Voluntary action indicated (VAI),** which means that deficiencies were identified, but these can be resolved by the company without the need for enforcement action.
- **No action indicated (NAI),** which means that no problems (or only very minor ones) were identified.

The district office will either issue an establishment inspection report (EIR) or, if advised, will take further action, such as issuing a warning letter. Warning letters are just one tool at FDA’s disposal to alert a firm to the fact its products are considered a risk to human health; therefore, authorities may take drastic action to safeguard patients (2). All warning letters are posted on FDA’s website and are visible to anyone interested, particularly the competition and customers. Making inspection reports easily accessible to the public is a peculiarity of FDA.

Redacted Form FDA 483s are available from FDA under Freedom of Information Act (FOIA) requests. Some commercial providers specialize in providing these at a fee.

What is the benefit of reviewing these documents, and what can you do with the information found? The rules and regulations (e.g., US 21 Code of Federal Regulations Parts 210 and 211) describe the requirements a company must comply with. There are, however, many aspects that are not described in much detail, such as how to perform complaints investigations, how to respond to inspection observations in an acceptable manner, and much more. What you can glean from Form 483s and warning letters is basically an interpretation of the regulations (i.e., the agency’s thinking and expectations).

What you can glean from Form 483s and warning letters is basically an interpretation of the regulations.

Of course, you need to filter the information and only review what may be relevant to your line of business. Still, there will be plenty of information that can help you avoid making costly mistakes. Bear in mind that the reported observation only tells part of the whole story, and there is much information, such as the actual product involved, that is confidential and thus not reported (i.e., redacted). As the observations on Form 483 are not classified, companies should take them all seriously. Not doing so could result in a warning letter, and that definitely would mean that the company is in trouble.

Making mistakes is human, repeating mistakes others made, and which have been reported in 483s or warning letters, is just plain careless and bad management. Unlike other regulatory agencies, FDA provides these valuable resources to anyone who cares to read them. It is a great opportunity for you to make good use of them.

References

Your opinion matters.

Have a common regulatory or compliance question? Send it to shaigney@mjlifesciences.com, and it may appear in a future column.
Smallest giant

The smallest cabinet housing a technological giant: The pioneering TOC-1000e is the first in the eTOC series of on-line analyzers for pure water applications. It combines ‘industry’s first’ technologies with high-sensitivity and easy-to-use advantages benefitting the efficiency and effortless handling demanded in pharmaceutical industry, semiconductor and precision manufacturing.

Breakthrough 'industry's first' technologies such as "Active-Path" flow line design and powerful, environment-friendly UV excimer lamp

Compliance with regulatory requirements such as the United States Pharmacopeia and 21 CFR Part 11

Smallest footprint supports flexible installation either as table-top, wall-mounted or pole-mounted version

Largest color touch panel providing exceptional visibility with simplified operation and data management

www.shimadzu.eu/toc-analysis/etocseries
Successful new oral treatments are built on the rigorous science of drug development and the art of accelerating your manufacturing path from clinic to market.

Catalent’s new OneXpress™ solution delivers streamlined development and manufacturing solutions to help transform your science into a successful treatment. Overseen by a dedicated program manager from start to finish, OneXpress combines phase-appropriate technologies and proven expertise, with scalable end-to-end capabilities throughout an extensive supply network, to achieve optimal accelerated manufacturing solution at every stage.