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Leader of the Pack?

AstraZeneca has potentially taken poll position in the race to develop a novel coronavirus vaccine, but will AZD1222 be ready in 2020?

AstraZeneca has potentially taken the lead in the current COVID-19 vaccine development race, through robust Phase I/II trial results and numerous deals being struck for supply, as well as media hype over a possible ‘fast track’ status in the United States, albeit denied by the company. So, will AstraZeneca’s hope of being able to deliver AZD1222 before the end of 2020 actually come true?

Positive outcomes so far

The AZD1222 vaccine is currently in late-stage Phase II/III trials in the United Kingdom, Brazil, and South Africa. Interim results from the Phase I/II trial, led by Oxford University, were released in July 2020 and demonstrated a robust antibody and T-cell response in all participants (1).

“The interim Phase I/II data for our coronavirus vaccine shows that the vaccine did not lead to any unexpected reactions and had a similar safety profile to previous vaccines of this type,” said Professor Andrew Pollard, chief investigator of the Oxford Vaccine Trial at Oxford University and co-author of the trial, in a press release (1). Further results on the immunogenicity and efficacy of the vaccine are expected to be available between September and November 2020.

Supply to meet potential demand

Since forming the partnership with the University of Oxford for the global development and distribution of the COVID-19 vaccine (2), AstraZeneca has established numerous agreements for the supply of the AZD1222 vaccine globally. For example, AstraZeneca and the European Commission recently concluded an agreement for the supply of up to 400 million doses (3), which adds to a prior arrangement the company had formed with the Inclusive Vaccines Alliance (4).

Additionally, supply and manufacturing agreements for AZD1222 have been set up with several partner companies, including Catalent and Cobra Biologics (5,6). AstraZeneca has been working on manufacturing the vaccine at scale to ensure broad and equitable access in the case of successful late-stage clinical trials and regulatory approval.

On a fast track … not yet!

US President, Donald Trump, is also reportedly pushing to get AZD1222 fast tracked through approval, so that it will be available to the US population before November’s elections. However, according to a report by The Independent, who spoke with AstraZeneca on the matter, the company has not been in discussions over emergency use authorization within the US (7).

“It would be premature to speculate on that possibility,” the AstraZeneca spokesperson told The Independent (7). “Late-stage Phase II/III trials for AZD1222 are ongoing in the UK and other markets globally, and we do not anticipate efficacy results until later this year.”

A cautious approach

Irrespective of the rapid pace at which companies, such as AstraZeneca, have been developing prospective vaccines and treatments to tackle the current COVID-19 crisis, clinical data and ultimately a thorough regulatory review are required. So, in terms of AZD1222, there may well be sufficient data by the end of the year to suggest efficacy and safety, but the regulatory bodies will still need to issue approvals before it can be used.

As reported in The Guardian, Professor Chris Whitty—England’s chief medical officer—has suggested that a vaccine may not be ready until winter in 2021 (8). Oftentimes, it is better to hope for the best, but prepare for the worst, and for vaccine development, sufficient data and regulatory review are critical requirements.

For now, stay alert, safe, and healthy.

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Regulations Under Regular Review

The 2020–2025 EMRN strategy will be regularly reviewed over the coming five years to accommodate science and technology advances.

The 2020–2025 strategy of the European Union’s medicines agencies network (EMRN) (1), covering licensing authorities in 30 states as well as the EU’s own European Medicines Agency (EMA), has been called a ‘living’ document.

EMA and the Heads of Medicines Agencies (HMA), representing national authorities, which published the strategy in early July 2020, warned that after the draft document is finalized in November 2020, following a three-month public consultation, its content and objectives will be subject to regular review. This review status is mainly because the next five years are expected to be a period of rapid advances in science and technology in medicines, particularly in the collection and processing of healthcare data.

The strategy gives unusual prominence to the regulatory response to the development and introduction of innovative production processes, especially for advanced therapy medicinal products (ATMPs) and continuous manufacturing by small production units. Also, the document has been published too early to incorporate all the important lessons to be learned from the shortcomings in the supply and application of drug treatments in the COVID-19 pandemic. Instead, these lessons will need to be inserted into the strategy at a later date.

Differences in approaches

Another major factor likely to trigger changes in the document is the EU’s Pharmaceutical Strategy for Europe (2), due to be published by the European Commission (EC), the EU executive, by the end of 2020. It will have a much broader and longer-term scope than the EMA/HMA strategy, extending well beyond regulatory matters so that it is more closely aligned with the EU’s current industrial and digital strategies, the European Green Deal (3) and, yet to be finalized, Europe’s Beating Cancer Plan (4).

The medicine’s network strategy, which will be followed by the EU’s 27 member states and three non-EU countries—Iceland, Norway, and Liechtenstein—covers issues such as medicines availability and shortages, supply chain problems, data analytics and digitalization, antimicrobial resistance (AMR), pandemics, and regulatory operational excellence.

The network’s strategy is mainly concerned with issues centred on the quality, safety, and efficacy of medicines, which, because of digitalization, is increasingly being extended to the provision of data of these aspects of pharmaceuticals. An important objective outlined in the strategy is for EMRN to become Europe’s trusted source for healthcare data.

The Pharmaceutical Strategy will ultimately be dealing with matters of policy and potential legislative changes.

To highlight the differences in approach of the network agencies and the commission, the network strategy document gives as an example the issue of new medicines, centrally approved by EMA, being withheld from certain EU national markets. Company-initiated limits on the distribution of centrally approved products for pan-European marketing has been pinpointed by regulators as a major cause of lack of accessibility to new medicines.

It would be the job of EMRN to ensure the marketing authorization holders (MAHs) are fulfilling their regulatory distribution obligations under EU regulations. If a MAH’s actions were for commercial reasons, then the commission may need to be involved because ‘political encouragement’ may have to be applied, as reported in the strategy document.

Manufacturing competitiveness

In a roadmap on the Pharmaceutical Strategy (5), the commission stated that a major objective was to increase the manufacturing competitiveness of the European pharmaceutical sector. The EU needed greater autonomy in the supplies of medicines, particularly in APIs for non-patented medicines in Europe, of which the vast majority come from China and India. The EC is considering proposing expansions in European production capacity, especially for APIs, backed by the development of innovative production processes.
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Hence, EMRN has concentrated on the laying of the regulatory groundwork for new manufacturing processes in the EU extensively in its strategy. A big driver is EC initiatives on the possible expansion of European pharmaceutical production capacity. These initiatives could includereshoring of some API manufacturing and the establishment of vaccine production units based on technological platforms for the development and production of vaccines in emergencies.

The network will also be considering the regulatory implications of the introduction of new process technologies, which have been under development over the past few years.

With personalized medicines, such as those based on gene and cell therapies, regulators are preparing for decentralized production in small manufacturing units, which bring the making of the treatment to patients. More drugs will be produced as a result in hospital pharmacies or operating theatres or even at the patient’s bedside. These small machines will be table-top size and mostly based on continuous rather than batch processes.

“At the moment, regulatory barriers or lack of harmonization of regulatory approaches is seen as a significant barrier to industry innovation and the take-up of new models such as continuous manufacturing,” states the strategy document (1).

Another area likely to see legislative changes is Substances of Human Origin (SoHo) because interfaces between tissue and cells and organs could affect the way plasma or tissues as starting materials, are regulated.

Advances in manufacturing processes and the introduction of production models using different types of locations will necessitate changes in good manufacturing practice (GMP) standards and guidelines. “Sustainable harmonized GMP guidance and supervisory procedures (conducted by EMA working groups) will be needed to provide a level playing field and a stable GMP regulatory environment with predictable outcomes,” according to the strategy document (1).

New manufacturing systems could hasten a shake-up in the implementation of good distribution practice (GDP) standards in Europe where the EU is already considering improvements. “The competences between authorities, especially as regards how GDP activities are authorized and supervised locally, are fragmented,” says the strategy document (1). “There should be consistent and comprehensive implementation of current GDP principles in all member states to ensure the integrity of the supply chain.”

Also, there will have to be changes in quality guidelines at the international level. The Geneva-based International Council for Harmonization (ICH) in pharmaceuticals is already planning a new guideline covering continuous manufacturing (1).

EMRN also envisages innovations in treatments and their production in the fight against infectious diseases, such as bacterial phages, monoclonal antibodies, and microbiomes, because of the enormous threat of AMR. AMR is considered to be a bigger danger by the regulators to human health than pandemics like COVID.

“If the emergence and spread of AMR spreads without restraint, the annual number of deaths worldwide is expected to increase to millions, making AMR a more common cause of disease than cancer by 2050,” the strategy document says (1).

To combat AMR effectively requires a ‘One Health’ approach combining human and animal health, the network asserts (1).

But this necessitates a massive degree of multidisciplinary collaboration between legislators, regulators, physicians, veterinarians, academia, the pharmaceutical and food industries, and agriculture. However, this sort of cooperation is needed to control pandemics as well.

The digitalization challenge
Perhaps in the short term, the biggest challenge facing the EMRN is the digitalization of the network or what it calls a ‘digital transformation’. This will not only require investment in IT infrastructure within and between agencies. It will also mean the building up of new capabilities among regulators and their staffs in data analytics so that they have full command of the potentially huge amounts of data that will be submitted by pharmaceutical companies in support of their marketing authorization applications.

Digitalization is already a major force behind improvements and innovations in pharmaceutical production processes. Furthermore, the network wants to create data storage and processing capacity that will help to make EU regulators the prime reference point for healthcare data. In particular, EMRN wants to make significant use of real-world data—data generated after a medicine has been marketed. These data will help fill some of the information gaps left by the narrow scope of clinical trials.

The EMRN concedes that there could be difficulties ahead with its digitalization programme because of a lack of existing regulatory standards and guidance on the use of patient data and artificial intelligence, already used in pharmaceutical development and production. Data science and its application has progressed far faster than regulations and guidelines.

The strategy document acknowledges that some national agencies are lagging behind with digitalization. Some authorities may have to achieve digital transformation more slowly than others.

A key issue will be the allocation of sufficient resources for digitalization both in term of funds and expert staff. Finance will have to be provided both by the EU and national governments.

Under pressure
EMA’s management board has complained about pressures on resources, although the matter was not specifically highlighted in the strategy document. Instead the strategy emphasizes the huge tasks facing the network as it confronts new scientific, technological, and social trends. “These challenges have never been greater,” the report confirms (1).

A lot will depend on the EC and its Pharmaceutical Strategy, which will be in a position to set the future policy directions of the whole EU medicines licensing network.

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Preventing Pandemic Vaccine Capacity

Rapid scale-up to billions of doses requires collaborative, all-out efforts by innovators, their manufacturing partners, and the entire supply chain.

Jennifer Markarian

The biopharmaceutical industry is working at unprecedented speed to develop and manufacture vaccines for the COVID-19 pandemic. Among the challenges of a pandemic is the need to scale up to billions of doses, at a larger scale than typically needed for vaccines, from raw materials all the way through to the materials for the containers for fill/finish.

Collaborative efforts to make a safe and effective vaccine against the novel coronavirus, SARS-CoV-2, are underway around the world. The timeline to develop, produce, and distribute an approved vaccine is being dramatically compressed, and companies are scaling up manufacturing ‘at risk’, making the vaccines before they have been approved. While pharmaceutical companies are bearing some of the risk, these efforts are being extensively funded by governments as well as non-profit organizations, such as the Coalition for Epidemic Preparedness Innovations (CEPI) foundation and Gavi, the Vaccine Alliance (GAVI). In the United States, the federal government’s Operation Warp Speed programme—a partnership among the US Department of Health and Human Services (HHS), the Department of Defense (DoD), and others—is investing in vaccine development and manufacturing, fill/finish capacity, and in capacity for supply of vials, needles, and prefilled syringes.

Scaling up capacity

Production of the billions of doses needed will require manufacturing at multiple sites, and innovators and contract development and manufacturing organizations (CDMOs) are partnering to come up with all the capacity that will be needed globally. Manufacturers know that it is not only the equipment, facilities, and raw materials—although these are necessary and require planning ahead—but also the knowledge and the expertise to run the process. Technology transfer is, thus, a crucial piece. Indeed, the tech transfer process is already underway at CDMOs.

Everyone is working at "pandemic speed," says Andre Goerke, head of the planning and value chain management business unit at Lonza; Goerke is also the global project lead for Lonza’s efforts to make the active ingredient for Moderna’s mRNA vaccine. The overarching challenge is to do what needs to be done in this accelerated timeline, but the team is unified in making it happen, he explains. "So far, the most significant asset has been the excellent integration of the Lonza and Moderna teams into a single group working for a common target," says Goerke.

Having adequate raw materials, building and staffing the facilities, and tech transfer are all keys to success. Flexible, modular facility designs allow manufacturers to adapt and move quickly. Goerke says Lonza’s Ibex...
facilities “have been set up with exactly this challenge in mind, to allow adaptation to manufacture different kinds of products. Adaptability allows us to cut construction time considerably compared to standard builds and gives the flexibility to install a broad range of manufacturing technology. In addition, we can plug into existing infrastructure, including services (gas, water, waste, etc.) as well as analytics and quality labs.”

Emergent BioSolutions says that its flexible CDMO capacity deployment model can respond quickly to demand fluctuations. The company’s Bayview multi-suite facility in Baltimore, MD is designated by the US HHS as a Center for Innovation in Advanced Development and Manufacturing (CIADM) and is designed to leverage single-use technologies to manufacture product in large quantities during public health emergencies. The CIADM can accommodate various types of vaccine platforms that can be manufactured in parallel. Four independent suites allow products or customers to move in and out quickly, explains Dino Muzzin, senior vice-president of manufacturing operations at Emergent BioSolutions. Platform-based equipment at the facility allows flexibility and facilitates tech transfer, noted Richard W. Welch, vice-president of development services at Emergent BioSolutions, in a presentation at BIO (1). Additionally, the company is adding new capacity at its Rockville, MD, and Canton, MA sites and expediting an expansion of its Camden facility in Baltimore, MD.

Pursuing platforms
Several types of vaccines are being developed and tested in the hopes that at least one, but possibly multiple vaccines and of different types, will be approved. The industry is counting on the advantages of ‘platform’ technologies, with development and manufacturing processes that can use the same or similar systems and equipment, tailored for different vaccines. Such platforms allow more rapid development and scale up and, even prior to the current pandemic, were predicted to be useful for responding to an outbreak caused by a new pathogen. mRNA vaccines. Nucleic acid-based vaccines—based on messenger ribonucleic acid (mRNA) or on deoxyribonucleic acid (DNA)—are examples of platform technologies. Moderna, Pfizer/BioNTech, CureVac, CarlSinObio, and others are making progress using mRNA platforms, with mRNA formulated in a lipid nanoparticle delivery vehicle. Inovio and others are working on DNA-based vaccines. Although nucleic acid vaccines have been tested in clinical trials, for Zika and Middle East respiratory syndrome (MERS), for example, none have yet been approved for use.

Moderna’s vaccine candidate, mRNA-1273, is encapsulated in lipid nanoparticles, and it has progressed to Phase III clinical trials. Moderna is building up manufacturing capacity, partly through its CDMO partner, Lonza, which is adding manufacturing lines in New Hampshire and in Visp, Switzerland. In an interview in late July, Goerke reported that tech transfer for the first step of the process has started as planned, and that preparation was well underway at the Portsmouth, NH facilities, with batches for the first of three process steps (the mRNA step) to be produced in July 2020. “Fit-out of our Visp facility is ongoing. We envisage the start of operations in Visp by the end of 2020,” said Goerke.

“Lonza aims to replicate the facility, equipment, and data management principles developed by Moderna,” adds David Callaert, head of global strategic growth investments and engineering at Lonza. “We plan to further strengthen and pragmatically ensure reliable supply through intense collaboration with the technical teams of Moderna. The aim is to achieve short processing times with high throughput. Going digital and maximizing the use of disposable equipment are some of the key components necessary to achieve these goals.”

Another CDMO partner of Moderna, CordenPharma, will manufacture large-scale volumes of Moderna’s proprietary lipids needed to make the lipid nanoparticle excipients. A challenge is the need to quickly scale-up by a factor of several hundred times the initial scale, says Matthieu Giraud, director, global peptides, lipids and carbohydrates platform at CordenPharma International. “We have to optimize the process for large-scale manufacturing and, at the same time, transfer to our larger assets. In addition, the scales are so incredibly large that we have to leverage our entire CordenPharma network to ensure a sustainable supply chain,” he explains.

The company’s facilities in France, Switzerland, and the US are working on the project; at CordenPharma Colorado, unique high-pressure chromatography systems usually used for manufacturing peptides have been reallocated for purifying lipids. Although making Moderna’s proprietary lipid at large scale is new, Giraud notes that CordenPharma has a long history of large-scale production of standard lipids using its platform technology. CordenPharma’s sister company, Weylchem Innotec, has been able to provide key raw materials for lipid production, Giraud adds.

Quality of the lipids is crucial because of the high proportion of lipids in relation to the mRNA. “The quality of the lipids is known to affect the encapsulation efficiency, liposome internalization by cells, and efflux rate of encapsulated therapeutic agents, all of which have implications for drug delivery and formulation shelf life. It is essential to create a very well-controlled process when manufacturing lipids,” says Giraud.

CordenPharma is on track to meet Moderna’s aggressive timeline, and manufacturing has started at three sites, says Giraud. He points to close collaboration between the company’s facilities, and he says that a rigorous risk management process identified gaps early on, so that risks could be mitigated.

Pfizer and BioNTech are also making progress on their lipid nanoparticle mRNA-based vaccine candidate,
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BNT162; initial results from Phase I/II studies are positive, and the companies are planning a global Phase IIb/III trial (2). Acuitas Therapeutics is providing lipid nanoparticles for the vaccine. If the trials go well, Pfizer and BioNTech plan to seek regulatory approval or authorization as soon as October 2020. Pfizer says it expects to manufacture 100 million doses by the end of 2020 and approximately 1.3 billion doses by the end of 2021. The US government placed an order for 100 million doses; the United Kingdom (UK) government signed an agreement for 30 million doses, both pending regulatory authorization or approval (3). Pfizer says it is building inventory of existing products now to make room for vaccine production later. Additionally, according to a Reuters report, Pfizer plans to shift some of its existing drug manufacturing to CDMO partners so that it can prepare for manufacturing the vaccine candidate at three facilities in the US and one in Belgium (4).

CureVac in Germany is also working on an mRNA vaccine, CVnCoV, and Phase I clinical trials began in June 2020 in Germany and Belgium. The company has a proprietary RNAoptimizer platform, which includes an end-to-end, good manufacturing practice (GMP) manufacturing process designed for mRNA-based drugs. The company is expanding its GMP facility and completing construction of its fourth production site in Tübingen, Germany. The company said the facility has the capacity to potentially supply several hundred million doses per year, depending on the human dose defined in the clinical trials (5).

In addition to its large-scale production facilities, CureVac is developing a small-scale, portable manufacturing ‘facility’ it calls The RNA Printer, which it envisions could be transported to outbreak regions or placed in hospitals. In early 2019, CEPI and CureVac announced a partnership to advance the automated equipment that can produce several grams of lipid nanoparticle-formulated mRNA, which could potentially be more than 100,000 doses, in a few weeks (6).

DNA vaccines. A challenge for distribution of mRNA-based vaccines is the need to keep them frozen. Inovio’s DNA-plasmid vaccine candidate, INO-4800, however, is stable at room temperature for more than a year and does not require being frozen in transport or storage, the company reports (7). Inovio announced positive interim Phase I results at the end of June and had hopes to begin Phase II/III over the summer. The company has a proprietary delivery device, the Cellectra 3PSP, that delivers the DNA-plasmid vaccine directly into the skin. An earlier version of the Cellectra has been used in clinical trials of Inovio’s DNA medicines.

Viral vector vaccines. Viral vector vaccines are another platform, which uses a live, attenuated virus as a vector or delivery vehicle for an antigen’s genetic code. A benefit of this type of platform is that the viral vectors are made with a standardized manufacturing process independent of the active part of the vaccine, noted CDMO Cobra Biologics (8).

Vaccines made with this type of platform from Merck, Johnson & Johnson, and CanSino Biologics have approvals for Ebola, and these companies are using their respective platforms for vaccine candidates against the novel coronavirus. China’s CanSinoBio’s viral vector vaccine for Ebola has been approved by China’s regulatory agency; the company’s vaccine candidate for the novel coronavirus uses adenovirus 5 (Ad5) and, as of 9 August 2020, was preparing to begin Phase III trials. Merck’s Ebola vaccine, approved by the US Food and Drug Administration (FDA) in December 2019, uses an engineered vesicular stomatitis virus (VSV) as the viral vector; Merck currently is working on a VSV-based COVID-19 vaccine. In addition, Themis, which was acquired by Merck in June, has a platform technology that uses a measles vaccine vector.

The Janssen Pharmaceutical Companies of Johnson & Johnson (J&J) received European marketing authorization for their two-dose viral vector vaccine for Ebola on 1 July 2020 (9). The first dose of this approved vaccine uses Janssen’s AdVac viral vector platform, based on adenoviruses that are genetically modified, so they are non-replicating in humans. The AdVac platform is being used for the company’s investigational SARS-CoV-2 vaccine, Ad26.COV2-S, recombinant, which moved into Phase I/IIa first-in-human clinical trials in late July. J&J’s goal is to manufacture more than one billion doses, and it is scaling up manufacturing capacity globally. On 5 August 2020, the company announced that the US government, through HHS’s Biomedical Advanced Research and Development Authority (BARDA), is committing more than $1 billion (nearly €846 million) for large-scale US manufacturing and delivery of the vaccine following FDA approval or authorization (10). The company said its partnership with CDMO Emergent BioSolutions for drug substance, announced in April 2020, was “the first in a series of prospective global collaboration agreements designed to accelerate manufacturing” (11).

The University of Oxford and AstraZeneca’s novel coronavirus vaccine candidate (AZD1222) uses a recombinant adenovirus viral vector platform that has been used in experimental vaccines for Ebola and MERS. Phase II/III trials have started in the UK, Brazil, and South Africa, and are planned for the US, with more than $1 billion (nearly €846 million) from BARDA for development, production, and delivery planned for fall 2020 (12). AstraZeneca has committed, so far, to more than two billion doses, in supply agreements with the UK, the US, Europe’s Inclusive Vaccines Alliance, the Coalition for Epidemic Preparedness, Gavi the Vaccine Alliance, and the Serum Institute of India (13).

Preparations for large-scale viral vector manufacturing capacity were picking up speed late in 2019 as the biopharmaceutical industry was beginning to address shortages due...
to the rapidly growing demand for viral vectors from the pipeline for cell and gene therapies and viral vaccines. Modular facilities and single-use systems are seen as one way to build capacity more quickly (14).

**Cell-based technologies.** While vaccines based on mRNA, DNA, or viral vectors are still new, recombinant DNA vaccines made in cell-based bioprocesses are another technology that offers the potential for rapid scaleup and have been in use on the market for several years. For example, the Flublok Quadrivalent influenza vaccine, initially approved by FDA in 2013 and acquired by Sanofi Pasteur in 2018, uses a recombinant DNA technology that combines the target DNA sequence in a plasmid with a baculovirus (BV) DNA, which produces antigens in a host cell; the antigens are then collected and purified to be formulated in the vaccine. These cell-based processes are more easily controlled and scaled than the traditional egg-based influenza vaccine production method, thus the recombinant DNA technology had been recognized for its potential as a response to a pandemic.

In December 2019, Sanofi entered an agreement with BARDA to increase its domestic pandemic influenza vaccine production capabilities in Swiftwater, PA. And now Sanofi’s platform is being put to use for the COVID-19 pandemic; Sanofi and GlaxoSmithKline (GSK) are partnering to produce a vaccine candidate using Sanofi’s S-protein COVID-19 antigen and GSK’s adjuvant technology.

Novavax’ recombinant nanoparticle vaccine platform uses recombinant BV to infect SF9 insect cells, which express the antigens that are then purified as multimeric nanoparticles. Although the company does not yet have an approved drug, the platform is used to make the company’s seasonal influenza vaccine candidate, NanoFlu, which received FDA fast track designation in January 2020. The platform is being used to make the company’s NVX-CoV2373 COVID-19 vaccine candidate, which is a stable, prefusion protein with Novavax’ proprietary Matrix M adjuvant.

Novavax received more than $1.6 billion ($1.35 billion) from BARDA to manufacture NVX-CoV2373 and stockpile raw materials needed for Matrix M (15). The company is working with Emergent Bio to manufacture both its NanoFlu seasonal influenza candidate and its COVID-19 candidate at Emergent’s Bayview, MD, facility. Novavax also announced a manufacturing partnership with CDMO Fujifilm Diosynth Biotechnologies (FDB) to make the bulk drug substance for NVX-CoV2373, and FDB’s site in Morrisville, NC, began production in July (16). AGC Biologics was contracted to manufacture the Matrix M adjuvant to expand Novavax’ capacity.

**Inactivated vaccine.** China’s Sinovac is using an even more traditional technology of an inactivated vaccine for its novel coronavirus candidate, CoronaVac. The company is building a commercial vaccine production plant that is expected to manufacture up to 100 million doses annually (17).

**The finish line**

The importance of fill/finish for vaccines is well known, and the supply chain is ramping up capacity for materials (including injection needles and the glass for vials) and for filling. CDMO capacity will be crucial in this stage, as well. Companies expanding capacity for fill/finish include Thermo Fisher Scientific; Emergent Bio, which received funding from BARDA and is working with four vaccine innovator companies; and Catalent, which is ramping up to support Janssen, Moderna, AstraZeneca, and others (18).

While the world waits for the results of the clinical trials for vaccines to prevent COVID-19 and, hopefully, regulatory approval or authorization of one or more successful candidates, pharmaceutical manufacturers are moving ahead with manufacturing at commercial scale, while also preparing to adapt to changes that arise, as development is also still being completed. The vaccine fill/finish line will, if all goes well, be the beginning of the end of the global pandemic.

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Tracki ng API Quality During a Pandemic

Risk-based decision-making is impacting all aspects of manufacturing quality from raw material supply to facility inspections.

Cynthia A. Challener, PhD, is a contributing editor to Pharmaceutical Technology Europe.

With additional safety protocols required in the manufacturing environment, gatherings of large people generally prohibited, and onsite inspections limited due to restricted travel, ensuring quality throughout the supply chain from raw material to API is more challenging. API producers have responded rapidly, implementing safety protocols, leveraging digital tools and technologies for virtual audits and inspections, and generally taking a reasoned, risk-based approach for making use of available resources.

In a time of crisis, risk-based decision making and strong leadership take on new meaning, according to David Waddington, NSF International’s executive director of pharmaceutical services for Europe, Middle East, and Africa. “It’s simply not possible for companies to operate their pharmaceutical quality systems (PQSs) and meet all their commitments with such a drastic reduction in available resources. Forward-thinking organizations have taken a proactive approach to deciding what activities can be stopped or delayed. Stopping an activity may seem to be extreme, but taking this decision proactively, before the quality system slips out of control, is a sensible approach,” he says.

For example, Waddington notes that change controls that have not yet been implemented could be halted without reducing validation effort, regulatory affairs work, quality control (QC) testing, and documentation updates. “Being extremely stringent with limiting change controls can free up (quality assurance) QA and QC resources,” he adds. Similarly, improvement plans such as introducing new systems could be halted, again freeing up resources. While delaying compliance activities feels wrong, Waddington says that in extreme situations it can be done using the quality system.

Activities that should be continued are those linked to batch release and testing. “It is important to ensure that there are sufficient QA/QC staff to support production activity and, if necessary, to reduce planned output. Deviations and out-of-specification/trend activities should also be performed in a timely manner to ensure product flow and also to identify any problems as early as possible,” observes Waddington. If action has been taken to stop some activities at the site and delay others, then, he comments, some staff may be re-deployed to bolster frontline staff.

“Taking a hard look at all activities that consume resources and applying a risk-assessment approach can help to free up some resources to bolster direct product fulfilment activities and thereby keep critical medicinal products flowing to patients,” Waddington concludes.

Early adoption of safety solutions

Because of the nature of pharmaceutical manufacturing and the need to ensure both operator safety and product quality, extensive systems and procedures are already in place at facilities producing pharmaceutical intermediates and APIs, including regular use of personal protective equipment (PPE) and good hygiene practices. Manufacturers, as a result, have been able to adapt quickly to new safety requirements and ensure continued supply of critical medicines according to current good manufacturing practices (cGMPs) and other regulatory requirements. This compliance is happening despite the challenges created by temporary plant shutdowns, the need for social distancing, and reduced on-site staff at a time of increasing production demands, complex supply chain challenges, and existing product shortages, according to Waddington. “It’s not uncommon for facilities to be operating with at least 30% less staff and key support functions, including QA, working remotely. Both companies and regulators are having to make some tough choices,” he says.

Fortunately, because API manufacturing is different from many other types of manufacturing, the need to exercise social distancing in these situations does not affect the nature of most processes, according to Jeff Ross, director of environmental health and safety for Cambrex Charles City (Iowa, USA).
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"Outside of the need for social distancing, Cambrex was an early adopter in implementing screening protocols for anyone entering the site. Today, employees are required to undertake a daily temperature check in addition to answering a series of health questions. Any visitors to the site must also go through the same process and need to complete a formal questionnaire," Ross says. Cambrex also performs job hazard analyses for all operational areas and makes recommendations on a variety of different elements in the typical workday, such as room capacities, the necessary frequency of sanitization, and the maximum size of any essential gathering.

Employee safety is always a priority for Thermo Fisher Scientific, and since the start of the COVID-19 pandemic the company has focused on protecting their health and safety while continuing to serve the needs of its customers, according to Vice President of Drug Substance Quality, Ben Gerlach. "Manufacturing safe APIs for medicines that can improve or save the lives of patients is both a large responsibility and a privilege. During the COVID-19 pandemic, we have continued to ensure the safety, efficacy, quality, and availability of the APIs we manufacture through a globally coordinated response, comprehensive site preparedness, employee training and communication, and robust business continuity planning," he comments.

Thermo Fisher Scientific manufacturing sites have specifically established increased hygiene protocols and tightened visitor guidelines. Stringent preventative measures developed in line with guidance from the World Health Organization, US Centers for Disease Control and Prevention, and local government agencies include restricting employee travel, encouraging remote work, enforcing social distancing, and requiring employees to wear masks at all times, according to Gerlach. For those employees who are on-site, the company keeps contact logsbooks, takes employees’ temperatures regularly, and employs a two-shift system for teams in the laboratories and on the manufacturing floor to accommodate social distancing. "As a result of the support, flexibility, and discipline of our colleagues and supply chain partners, as well as the IT infrastructure available, all Thermo Fisher API manufacturing sites have remained operational since the start of the pandemic with continued GMP compliance," Gerlach remarks.

Close communication with suppliers
Key to ongoing provision of API to pharma customers is effective management of the supply chain, including assurance that materials continue to meet the high-quality standards of the pharma industry. Prior to the COVID-19 pandemic, many API manufacturers made use of international industry conferences to meet with their vendors and customers, from raw material producers to contract research organizations, and contract development and manufacturing partners. Travel restrictions and the prohibition of large gatherings, both designed to limit spread of the SARS-CoV-2 virus, have forced API producers to find other means of keeping track of the supply chain. Despite being unable to attend major industry conferences in-person, representatives of Thermo Fisher Scientific have joined events virtually and maintained close communication with supply-chain partners to ensure there is no change in quality or availability of raw material, according to Gerlach. The company’s regional teams monitor the COVID-19 situation, particularly in Asia, Europe, and North America, where most of its qualified suppliers are located. "We also continue to closely track our purchase orders and have put a major focus on regional governmental restrictions that could affect manufacturing and shipping and the timely availability of raw materials and critical equipment so there is no lapse in our ability to help customers bring important medicines to market as fast as possible," Gerlach says.

Before the pandemic, Cambrex had prepared for emergencies and crisis situations by undertaking strategic logistics planning and implementing response processes, according to Ross. “Over the past several months, we have been working strategically to expand the supply chain globally by evaluating suppliers across the globe, including those in the [European Union] EU or US. Expanding our footprint and ensuring supply chain redundancy has enabled us to minimize the risk of supply chain interruptions and work with partners efficiently,” he explains.

Because of the circumstances connected with COVID-19, Ross also stresses that it is extremely important to frequently engage with supply chain partners to ensure that Cambrex understands the impact of the pandemic on their businesses and any potential downstream effects on Cambrex’s unit operations that might ensue. "Video conferencing and more frequent communications have been important for our continued visibility into the supply chain," he asserts.

Effective communication, which Waddington says involves listening more and speaking only when there is something valuable to say, has enabled NSF International to successfully transition from a training, consultancy, and auditing service provider that operated primarily face-to-face with clients to one that can now provide true virtual and blended learning, remote audits, and consultancy. “We believe we have achieved a truly remarkable transition in such a short time frame, as have many of our pharma industry clients,” he states.

Leveraging digital tools and technologies
That rapid transition has been made possible by leveraging a wide range of digital tools and technologies in new ways and to a much greater extent than API manufacturers and their suppliers and customers were previously accustomed to. The most obvious change, according to Waddington, is the reliance on digital meeting platforms. “We have seen
a significant increase in the need and willingness for more regular video calls and sharing of documents and information through secure file handling platforms,” he observes.

As part its digital transformation strategy, Thermo Fisher had already implemented digital tools to support many of its GMP processes, and many of these systems have proven to be highly beneficial to ensuring continued API quality, according to Gerlach. For example, Thermo Fisher uses Documentum (OpenText) to store GxP documentation and manage the creation, amendment, approval, use, and retention of all documents. The company also uses tools to manage quality events and support training and virtual communication and systems for electronic process control and data analysis. Cutting-edge camera and augmented reality (AR)/mixed reality technology is also leveraged to provide safe, virtual access to Thermo Fisher facilities.

Cambrex has also invested heavily in recent years in information technology platforms and advanced technologies that have enabled the company to maintain its current quality systems while allowing remote working for staff and facilitation of virtual collaboration with internal and external stakeholders, according to Chuck Walker, director of regulatory compliance at Cambrex’s Charles City facility.

Examples include live broadcasting from Cambrex’s manufacturing sites and clients being able to remotely visit its facilities, have instant interaction with subject matter experts, and undertake live-virtual audits. “When lockdown conditions were implemented at our multiple sites, we saw immediate results from these investments in that our employees were able to operate as usual from remote locations; client visits became virtual; and we were still able to undertake internal and external audits,” Walker observes.

In fact, from an auditing perspective, NSF International has witnessed a major shift with companies allowing the use of camera technology within facilities to share images, according to Waddington. “This approach is a real game-changer as it transitions from a virtual ‘desktop’ audit to a true interactive remote audit, allowing the auditor to view operations live and assess effective implementation of the PQS including remotely observing facility design, hygiene, and even operator behaviours,” he explains.

**Detailed virtual inspections**

Such digital tools have also been invaluable for regulatory agencies during a period when most onsite inspections have been halted due to the COVID-19 pandemic. Many agencies have historically conducted some form of remote risk-based review or ‘desktop’ assessment, so in some respects their current approach is an extension of that process, according to Waddington. One additional challenge that regulatory authorities have had to face, though, is to ensure the processes they are following have legal standing in line with legislation in place in their respective countries. “A number of agencies, including the [United Kingdom’s Medicines and Healthcare products Regulatory Agency] UK MHRA, have been successfully conducting very detailed remote inspections of facilities and have been able to follow up on for-cause audits and ensure remediation programmes are progressing in line with company commitments,” he says. The use of AR technology, Gerlach adds, enables Thermo Fisher to provide regulatory agencies unprecedented access to its facilities without them needing to be physically present. “Auditors can navigate through the facilities and perform factory acceptance tests. Remote assist provides the means to facilitate support both internally and externally from anywhere in the world,” he says. “Limiting onsite visits helps protect both employees and visitors without impeding operations or impacting quality,” Gerlach continues. “All of these solutions are made possible with training from the augmented execution team and tremendous collaboration from our sites, vendors, clients, and regulatory agencies,” he concludes.

Cambrex deployed virtual live tour technologies throughout its facilities when lockdown and restricted access conditions became applicable. “These technologies have enabled both client audits and regulatory audits to continue,” Walker says. “Although we have not had any direct regulatory requests during this period at our Charles City facilities, many of our other sites in different locations have successfully undertaken virtual audits, and we are fully prepared for live virtual audits if needed here at Charles City,” he notes.

**Innately prepared**

In fact, Walker believes that the API industry in the United States is innately equipped to manage the COVID-19 pandemic given the governing force behind employee protections with US Occupational Safety and Health Administration’s industrial standards. “Because safety is already so deeply engrained in our daily operations, along with engineering controls, we have been able to operate confidently knowing we are protecting our employees and product simultaneously,” he asserts.

API manufacturers have also invested in expanding capacity for specialized intermediates and APIs in recent years, which has also contributed to the ability of contract service providers to meet growing demand during the pandemic.

**Silver lining?**

As horrible as the COVID-19 pandemic has been and continues to be, it, like all crises, has presented opportunities for improvement as well. "If there is a silver lining to the current situation, it will lie with those employees who stepped forward for their colleagues and found creative ways to get things done. Or it may lie in the cross-training of employees for new or expanded roles,” Waddington states. For instance, he points out that key decisions around product quality may be delegated closer to the unit operation, which should result in efficiency gains. **PTE**
Moreover, as microbiota normally requires enteric protection these capsules are also optimized for enteric coating or coating for targeted release. A capsule that already provides a certain degree of enteric protection could be another option, dependent on the specific needs of the therapeutic entity or formulation. In summary, there is no reason to exclude any type of formulation in a capsule dosage form. Working closely with the capsule supplier and using their expertise and capabilities throughout development and manufacturing is encouraged.

Beneficial features
PTE: What beneficial features can capsules offer over other dosage forms?

Stegemann (ACG): The most important thing is that you first establish a comprehensive target product profile (TPP). This should also include the targeted patient profile and should take into account that according to the International Council on Harmonization (ICH) Q8 guideline, ‘in all cases, the product should be designed to meet patients’ needs and the intended product performance’ (1). These TPPs will guide you in selecting the best dosage form for the specific product.

Looking at the actual industrial and regulatory trends, some particular capsule features are gaining importance. For example, 60% of new drug launches in 2019 by the FDA [US food and Drug Administration] were designated in one or more expedited categories of fast track, breakthrough, priority review, and/or accelerated approval (2). The very tight timelines in development favour the use of simple, yet effective, capsule formulation development.

Increasing focus on a special population, such as paediatric or geriatric patients, require a higher number of different dose strengths, easy to swallow forms like sprinkles,
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and, to address the issue with increasing polypharmacy, the provision of fixed-dose-combination products. Without compromising on the release characteristics, multiparticulates (e.g., pellets, mini-tablets) manufactured at large scale, can be customized to serve any of these populations and needs by capsule filling. Different sizes, colour combinations, and imprints will make these customized products unique. Or, take for example, inhalation drug therapy, where capsule-based dry-powder inhaler (DPI) products are the most cost-effective form, and can be manufactured on standard capsule filling equipment that is available around the world.

Disadvantages to consider

PTE: Are there specific disadvantages of capsules over other dosage forms?

Stegemann (ACG): As for any dosage form, there are advantages and disadvantages that need to be balanced against each other during the TPP process. Probably, the most significant disadvantage occurs when formulators are initially requested to develop a tablet formulation. When this dosage form is not feasible due to technical reasons, the formulators are then requested to push the formulation into a capsule. Even though it might work, the formulation is normally suboptimal for capsules, leading to a lot of issues along the commercial phase, which is then perceived as a general capsule dosage form problem.

Another disadvantage is that for a high dose formulation, the capsule size might become prohibitive. In my experience, patients generally do not want to accept larger, brick-like tablets and, as a result, tend to crush the tablets or capsules for administration. For cases where the largest (size #000) capsule might be required, why not instead consider employing a sprinkle formulation, which can be administered with soft food that the patient prefers?

Accelerating development

PTE: How can capsules aid in speeding up drug development timelines?

Stegemann (ACG): More than 25 years ago, when I began my career in capsule science, there was a collaborative effort that led to the formation of group basics for capsule formulations (3), which are absolutely still valid today and have substantially evolved with new types of capsules and excipients. Not surprisingly, drug in a capsule alone, or a simple blend, is still the preferred approach for the first-in-human trials. The majority of these Phase I formulations are already achieving the desired performance and remain in capsules for the fast track or breakthrough therapies through to the market.

“There is no reason to exclude any type of formulation in a capsule dosage form. Working closely with the capsule supplier and using their expertise and capabilities throughout development and manufacturing is encouraged.”

—Sven Stegemann, ACG

And to be a little bit provocative, we as pharmaceutical scientists prefer more challenging formulation programmes than applying a simple blending and encapsulation process. However, with the increasing cost pressure, it is inevitable that we will be increasingly questioned regarding the over-engineering of products in development.

Soft versus hard gel

PTE: What are the advantages and disadvantages of soft gel versus hard gel capsules?

Stegemann (ACG): This question suggests that I can use soft gel or hard gel for any type of formulation and that these dosage forms are interchangeable from a technical standpoint, which is not necessarily true. However, looking at the liquid-filled products on the market in soft and hard gels, we see very different portfolios. For example, soft gels are suited for hydrophilic liquids, but they are not suited for hot melt products. Hard capsules can also be filled with combinations of liquids and solids, like pellets, smaller capsules of tablets. Only oily formulations are suitable for both soft and hard gels.

With regard to the capsule polymer, pharmaceutical soft gels are still gelatine-based, while liquids and hot melts can be filled in a hard capsule made of gelatine or HPMC. Whereas, the shell composition of soft gels can be adapted to tailor the shell to certain formulations. When we consider all of this, we are talking about two distinct and complementary technologies and dosage forms, that can generally not be interchanged without reformulation.

Substantial innovations

PTE: Are there any significant innovations in capsule formulations that you believe have impacted industry or will in the near future?

Stegemann (ACG): Pharmaceutical sciences will continue to be one of the highly dynamic sciences. There are many innovative formulations and drug delivery technologies under investigation, and only clinical evidence and real-world data will give us the final answer.

One of the areas where we see substantial innovation right now is in the field of enhanced therapeutic entities, so-called 505(b) (2) or hybrid applications. Known drugs are being reformulated using advanced drug delivery technology to achieve a better ‘effectiveness’ (efficacy under real-world conditions) and drug safety, by reducing medication errors.

Many innovations are taking place in the field of capsule-based DPI. The delivery of high drug doses and large biomolecules, enabled
by particle engineering (e.g., spray drying), provide new avenues to treat now life-threatening diseases, such as cystic fibrosis.

Looking toward microbiome research and the microbiota as the therapeutic entity, capsules will be the preferred choice and become a functional excipient, protecting the sensitive microbiota from moisture, as well as gastric juice, and releasing it at the defined site of the intestinal tract.

Regulatory considerations

PTE: Are there specific regulatory considerations surrounding capsule formulations?

Stegemann (ACG): Capsules are well-known and, regulatory-wise, a well described and accepted dosage form. Nevertheless, regulatory science continues to drive towards more global quality standards, digitalization, and patient focus and centricity. If we just look to digitalization, we see global efforts to combat falsified or substandard medicines by tagging and tracing each box and, soon, each dosage form from the factory through to the patient. The increasing focus on patients and patient centricity stems from the patient’s growing awareness as one of the most important factors in achieving the therapeutic outcomes.

Starting with the geriatric population, the European Medicines Agency (EMA) has put forward another reflection paper on the pharmaceutical development of medicines for use in the older population (4), followed by an FDA initiative of patient-focused drug development (5). All these regulatory and industrial initiatives require much more trans- and multidisciplinary collaboration, including the pharmaceutical supply industry. The next generation of capsule products to serve these emerging regulatory and industrial requirements will definitively benefit from co-development, if not co-creation, in close partnership with capsule manufacturers.

Pandemic response

PTE: What impact has the COVID-19 pandemic had on capsule formulation, if any?

Stegemann (ACG): As a result of SARS-CoV-2, the pharmaceutical industry will go through a complete rethink of the pharmaceutical supply chain and the relationship with suppliers over the next two to three years. The revival of more regional and flexible manufacturing, as well as further governmental cost pressure, will raise several questions on investments into efficient manufacturing infrastructure. This manufacturing adjustment will be another opportunity to consider capsules due to the simplicity and flexibility in capsule product manufacturing and other innovative approaches, such as continuous manufacturing.

Editor’s Note: Use of Nanoparticles for Intranasal Delivery of a Water-insoluble Drug

A peer-reviewed article, “Assessment of Nanosuspension Formulation for Intranasal Administration” has been published in the September 2020 issue of Pharmaceutical Technology North America and is available on PharmTech.com.

In the paper, the authors summarize research performed at Dr. Reddy’s Laboratories in India, to develop a stable nanosuspension of celecoxib, a drug that is poorly soluble in water. The researchers examined the impact of the drug’s particle size distribution on its pharmacokinetic parameters following administration intranasally in adult male rats.

Tests were run to characterize an optimized prototype formulation based on particle-size distribution, crystallinity, pH, osmolality, and shelf-life stability, and the suspensions were tested for pharmacokinetic parameters following administration.

Results of the research suggest that intranasal administration of nanosized particles demonstrated significant benefits when compared with micron-sized particles, for achieving rapid T$_{max}$, which corresponds to the amount of time that a drug is available in the body and the maximum concentration. The nanosuspension also resulted in better AUCs (i.e., partial ‘areas under the curves,’ which correspond to the variation in a drug’s concentration in blood plasma over time). The work also demonstrated the first documented use of an in-line high shear homogenizer to prepare the nanosuspensions.

Based on their work, the researchers determine that nanosuspensions in intranasal delivery forms could be an effective approach to formulating water-insoluble drugs similar to celecoxib, for treating chronic health problems.

Article Authors

Sandeep S. Zode, Rajesh Patil, Piyush Gupta, Rajasekhar Jaladi, Anirudh Gautam, and Rajeev Raghuvanshi

—Agnes Shanley
Best Practices in Manufacturing Drug–Device Combination Products

Jennifer Markarian

Designing and then manufacturing a drug–device combination product is a complex process that must take into consideration variables in manufacturing the drug delivery device, such as an inhaler or an autoinjector, as well as interactions between the drug and the device. Phillips-Medisize, a Molex company, has both clinical and commercial manufacturing facilities for drug–device combination products, and the company is expanding its Global Innovation and Development site in Struer, Denmark by adding a dedicated unit for manufacturing development. Pharmaceutical Technology Europe spoke with the company’s experts: Justin Westendorf, product development manager; Bryan Moris, director of Global Pre-Production Quality; and Chris Conger, director of Connected Health Device Technology, about some of the best practices in manufacturing drug–device combination products.

Development best practices

PTE: What are some of the best practices in moving from clinical manufacturing to commercial manufacturing of a drug–device combination product?

Westendorf (Phillips-Medisize): During the design development process, there must be a good partnership and engagement between the device development team, formulation development team, clinical team, and the regulatory team. When scaling from building 500 units to 10,000 units to 10 million units, the device design can often undergo significant evolutionary changes. All stakeholders need to be aligned on which areas are allowed to change (such as assembly features) and which areas have to be locked down early (such as drug contacting features), as well as when features must be locked down to protect the integrity of the data being generated throughout the device development lifecycle.

It’s important to point out that there are perspective differences between a commercial manufacturing team and a product development team. When building products in commercial manufacturing, devices are built with the expectation that if the components and assemblies are produced to specification, then the performance requirements of the device will be met for the intended use population. In product development, however, the need for product may come before the design or manufacturing processes are well established or controlled. There are more nuances associated with ensuring the design and the drug formulation will successfully work together in these early builds.

For instance, there may not be time or value in performing process validation for early builds when the design is still evolving. This situation requires a flexible but compliant quality management system to work with stakeholders on a risk-based approach to controlling early device builds. In addition, how users will use the product must be assessed. This means getting device samples into users’ hands to study how they interact with them in the context of specific environments. If it’s determined that there are points of confusion that could lead to use errors and harm, regardless of drug performance, the design team will need to make adjustments to the design. By the time a product gets to commercial manufacturing, all of these types of questions have been answered by a robust design development process.

PTE: What are some of the concerns for choosing materials for the device in a drug–device product? Do you need to evaluate potential interactions between the drug and device?

Westendorf (Phillips-Medisize): Physical interaction with a user is one concern. It’s important to understand the intended use and use environment and make sure you’ve identified how the user will interact with the product. Possible product component interactions with the user’s hands, skin, mouth,
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nose, and other areas of the body, should be taken into consideration. Materials need to be assessed for the potential risks they may pose to the user.

Drug interaction also must be considered—especially for inhalers, where there are very small, often organic, charged molecules that are flowing through a pathway that’s typically plastic and may also be charged. These types of interactions can have an impact on how—and how much—of the drug exits the device. It’s also important to understand the chemical interactions to make sure nothing from the components could leach into the drug or change its chemistry.

Manufacturing is another consideration. Every component will be manufactured via some means (e.g., machining, injection moulding) and likely be assembled using some technology (e.g., adhesive, laser welding). A key variable in material selection is the compatibility between the material, the desired manufacturing method, and assembly to other components in the device.

Early in the design development process, candidate materials are identified. But then tools and evaluation techniques must be employed to gain confidence in those candidate materials. At this point, it may become apparent that a material change is required, perhaps because structural performance is lacking or clinical performance is falling short, or it could simply be difficult to make a device component with that material.

‘Material selection’ isn’t an event that happens, but rather a maturing of the design and better understanding of the materials and how they interact with the drug and the patient and how suitable they are for the intended manufacturing processes. This understanding improves as the design is progressed through later stages of the development and verification testing process to reach a point where the component materials have been demonstrated to meet performance and manufacturing requirements.

**Controlling quality**
PTE: What are some best practices for quality assurance (QA)/quality control (QC) of drug-delivery device manufacturing? What are some of the factors that need to be tested that are unique to a drug delivery device?

**Moris (Phillips-Medisize):** When it comes to drug delivery devices or combination products, it’s really about control—control of the product and control of the components going into it. A high level of control is required, but that can mean many different things. It could refer to additional levels of training or processes and procedures that are well-vetted to ensure control over the drug itself, whether it needs to be filled into a container or in containers that are already prefilled.

A high degree of control is paramount when going from clinical manufacturing to commercial manufacturing. Designing processes and having conversations up-front based on best practices for controlling the device and the drug, from both a clinical and volume manufacturing standpoint, are important. For example, when working with different dosages, it is useful to ensure a unique vial labelling or colour-coding system exists to help minimize the potential for a mix up.

It is also important to ensure a fool-proof shift from labour-intense, detailed, and manual clinical processes to automated commercial processes. The process must be carefully designed from the beginning, so that when it does ramp up and a product goes to many global commercial sites, success is assured. Because, ultimately, the product is being designed for commercialization.

The fact is, there will be variations in the production of the device—from device development to the manufacturing process to final refinements in commercial manufacturing. That’s why it’s important to uncover, on the front end, where variation can occur and how that variation might impact drug delivery performance. Then it’s crucial to take that a step further by characterizing how the variation that’s expected in commercial manufacturing will impact drug delivery performance. Skipping this characterization step can negatively impact the investment around, and commercial success of, the device.

**PTE:** What are some of the risks for a drug delivery device that should be considered in manufacturing?

**Westendorf (Phillips-Medisize):** There are companies that will take an ambitious approach to development, and they may not capture or understand the risks and potential impacts. This approach results in residual risk making its way into the commercial manufacturing environment. Then there are companies that take a more conservative approach to reduce the risk of potential supply chain interruption in commercial manufacturing.

The biggest risk to commercial manufacturing is the investment and effort—or lack thereof—made in design development and the manufacturing development that should occur in parallel to development. If time is spent focusing on de-risking the technology piece, but not much time spent on finding sources of manufacturing variation and de-risking them during design development, residual risk will be passed into the commercial environment, where a combination of variations in manufacturing processes is unavoidable.

There can be an investment impact, especially pertaining to schedule and price. When collaborating with customers to construct a design development proposal, it’s therefore important to understand their approach to risk-based decisions and what they consider important. Some are more willing than others to accept a certain...
A further advantage of lyophilization lies in the fact that the process requires low temperature and so is suitable for heat sensitive drug substances or those prone to degradation from hydrolysis, Morbey continues. “Other advantages include the ability to reconstitute to the desired concentration at the time of use and reducing shipping costs due to lower finished product weight compared to liquid products,” he notes.

A challenge for lyophilization is that not all molecules are stable as freeze-dried solids. “For example, some cephalosporins remain amorphous and are less stable than when in the crystalline form,” stresses Sacha.

For Morbey, a major disadvantage of freeze-drying is the development of appropriate formulations that are suitable for lyophilization. “Not all liquid formulations are suitable for lyophilization,” he confirms. “The appropriate buffers, cryoprotectants, bulking agents, and tonicity modifiers need to be carefully selected to provide both stability to the formulated drug substance and properties suitable for lyophilization.”

“Volatile compounds, such as acetate buffers, can be removed by high vacuum, which can result in changes of the final product pH,” notes Sacha. Additionally, he specifies that not all solutes can be dried to a form with an acceptable appearance. “For example, formulations prepared with high salt concentrations have low melting points and are difficult to freeze-dry,” he says.

Development of the lyophilization cycle can also be challenging, requiring extensive expertise, particularly for turnkey projects, highlights Reuter. Each cycle is unique to the formulation and requires expertise to ensure product quality, agrees Morbey. “Most cycles are 24 to 96 hours; however, some products require conditions that extend the cycle length beyond 192 hours. A consistent challenge to lyophilization is the expertise required to develop a cycle appropriately to fit both equipment and product limitations,” he states. “Some lyophilization cycles are not suitable for commercial scale lyophilizers.”

Advantages and disadvantages

Stephan Reuter, managing director, Optima Pharma in Gladenbach-Mornshausen emphasizes that the greatest advantage of lyophilization is the stable formulation result, which subsequently impacts the success of a development programme. “The development of drugs is a very costly and time-consuming process, and always runs the potential risk of not being successful,” he says. “Many substances would not be stable without freeze-drying technology, which creates a durable product and retains effectiveness.”

Additionally, as the formulation is filled as a liquid, there is compatibility with almost all filling lines and little variability occurs as a liquid formulation is amenable to maintaining proper fill weights, asserts Gregory Sacha, senior research scientist, Baxter BioPharma Solutions. “Sterility of the product can also be maintained and achieved,” he says. “The moving parts of the equipment, such as compressors, are located in an equipment maintenance area on the other side of the aseptic manufacturing area. This keeps the area clean and reduces introduction of foreign particles.”

The general principle of lyophilization has hardly changed, but significant advances have occurred in process and product attribute understanding.

Felicity Thomas

Lyophilization is a well-established technique within the bio/pharmaceutical industry and is a necessity for certain drug products that include unstable ingredients, require longer shelf-lives, or are temperature-sensitive. The lyophilized drug market is expected to grow at a compound annual rate of approximately 7%, according to market research, mainly driven by increasing regulatory approvals for lyophilized formulations (1).

“The primary benefit of lyophilization is improved product stability,” explains Andrew Morbey, associate director of process development, LSNE Contract Manufacturing. “This can manifest as additional shelf-life at frozen, refrigerated, or ambient storage conditions or as equivalent stability at an increased storage temperature. In many cases, this eliminates the need for cold chain shipping and storage, reducing risk during manufacturing.”

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because there is little consideration for refrigeration capacity, system capabilities, or variation in equipment capabilities. Without the awareness of these challenges, there could be considerable impact to the product.”

**Traditional technique but advancing process understanding**

“There have been few changes to lyophilization equipment, but there have been large changes in understanding and conducting the lyophilization process,” remarks Sacha. “For example, process development was achieved by trial and error and, in some cases, it still is. However, today process development is often approached using the first principles of heat and mass transfer to understand the process.”

Understanding the process involves a thorough thermal characterization of the formulation so that the failure point during primary drying can be known, continues Sacha. Additionally, an understanding of the capability of the equipment, determining the heat transfer coefficient for the specific vial, and determining the resistance to mass transfer of the drying solid are required. “The data are used to develop a design space for primary drying that identifies the most efficient process conditions, as well as the conditions that may lead to failure of the product,” Sacha adds.

Morbey agrees that despite the lack of changes in the lyophilization process over the past 15 years at a commercial scale, the laboratory and academic settings have seen great advances in the understanding of each individual step of the process and the impact on product critical quality attributes (CQAs). “These advancements include controlled nucleation to improve the thermal treatment phase,” he says. “Understanding of container specific heat transfer coefficients, mass flow and heat flux, and implementation of process analytical technology (PAT) devices to aid in primary and secondary drying end point determination have supplemented the development of the drying phases of lyophilization.”

Significant advancement toward the automatic loading/unloading systems have been seen throughout the supporting manufacturing activities, Morbey continues. These advancements have limited the need for operator intervention and, hence, mitigated risks to sterility. And, isolator technology has also advanced, he adds.

“The development of freeze-drying technology is based on product development, since freeze-drying has a massive influence on the product. Therefore, innovations must be adapted to product development,” reveals Reuter. “This reasoning is why the general principle of freeze-drying has not changed in the last 30 to 40 years, but freeze-dryers have become faster and more effective. They are more accurately adjustable, and alternative, more environmentally friendly refrigerants are increasingly being used.”

It is possible to drastically reduce processing time by building a primary drying design space based on the first principles of heat and mass transfer, emphasizes Sacha. “Data obtained through this design space can also be used to support deviations in shelf temperature and chamber pressure that may occur during routine production,” he says. “The technique also demonstrates that the company has a good understanding of the equipment and how the formulation can affect processing conditions.”

“The simulation of processes during freeze-drying and their influence on each other can give a better understanding of the process itself,” adds Reuter. “The integration of the products’ properties in the simulation, which has to be freeze-dried, allows improvements in the process by predicting what the product quality attributes will be at the end of the freeze-drying. So, nowadays it is theoretically possible to define lyophilization process parameters with very high accuracy. If the freeze-drying parameters are defined correctly, the entire process achieves the best efficiency.”

However, verification and qualification of the process are still required, Reuter continues, which leads on to the instrumentation. “A number of new sensors are available now on the market to monitor and control the lyophilization process with very high accuracy,” he explains. “Through these sensors it is possible to save time and energy, and, hence, make the process more efficient.”

The majority of equipment advancements were created to aid in the development, optimization, and characterization of lyophilization cycles so that it would be possible to effectively transfer cycles to commercial-scale equipment, emphasizes Morbey. “Most drug product manufacturers do not have the luxury of performing lyophilization cycle development activities on the intended commercial-scale freeze-dryer. Therefore, a comprehensive understanding of the product’s characteristics and equipment is required to ensure product quality is maintained when scaling up to commercial-scale production,” he says. “Product characterization using modulated differential scanning calorimetry and freeze-dry microscopy is now standard practice. New technologies are being developed to supplement these tests and better understand the product.”

Equipment process improvement for analytical technologies include tunable diode laser absorption spectrometry, heat flux measurements, end of primary drying determination, and in-line mass spectrometry. Morbey continues. “Implementation of these technologies during the development phase, in most instances, has increased the overall time, energy, and cost of development services. However, the benefit is realized through seamless transitions from development scale to production scale,” he notes. “Complete process and product understanding following quality-by-design principles takes time; however, a standardized approach for lyophilization cycle development together with experienced scientists capable of utilizing the available PAT devices can streamline the development process.”
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Biologics and highly potent compounds
An additional growth factor for lyophilization is the rising proportion of biologics in development pipelines. “The industry evolution toward biologics is making the need for lyophilization more prevalent,” confirms Morbey. “Many biologics are not stable in solution and, as such, need to be lyophilized.”

Morbey iterates that there are even some instances where lyophilized biologic drug products form aggregates on stability. In such cases, it is necessary to revisit the formulation and add surfactants or additional excipients so that the aggregation is inhibited. Formulation scientists should be able to build upon previous experiences to inform development activities prior to the issues arising, he notes.

“The high cost for biologic drug substance development and manufacture translates to smaller drug product batch sizes in order to reduce risk. For lyophilization development scientists, this enforces the importance of formulation and cycle development to ensure minimal product loss,” Morbey stresses. “Some high-volume parenteral manufacturers may be accepting of 90–95% yield from 200,000+ unit batches when producing 30 million units a year. For low volume, high-value lyophilized biologics every dose is important. Unnecessary manufacturing line loss and rejects caused by inadequate lyophilization practices are not acceptable.”

For Sacha, the increased need for lyophilization as a result of the rising proportion of biologics will be a long-term effect unless combinations of excipients are developed that can offer the same, or better, stability improvements as freeze-drying. “The challenge with freeze-drying biologics is that they can be sensitive to the stresses of freezing and drying” he says. “This issue requires study of the biologics’ sensitivity to interfacial interactions and loss of residual moisture to determine if certain protective agents are needed in the formulation.”

Turning the attention to highly potent compounds in general, Reuter notes that the processing of such pharmaceuticals puts special demands on the cleaning concept and construction of pharmaceutical plants so that safety of both the product and human life can be assured. “It is, therefore, important to develop a comprehensive and holistic process for the filling and processing of highly potent substances, including comprehensive pressure and wastewater concepts, for example,” he adds.

“Many of the highly potent molecules are both poorly soluble in aqueous solutions and unstable in solution. There have been a rising number of requests to lyophilize formulations that consist of 100% organic solvent or co-solvents,” Morbey says. “Lyophilization of organic solvent systems provides unique challenges to the development programme and its equipment. The handling of the formulation and compatibilities of the material contact and equipment, need to be fully understood.”

Additionally, the development scientist must comprehend how to remove the organic solvents from the cake to residual levels without affecting other product quality attributes, asserts Morbey. “Hopefully, the trend towards higher value biologics and highly potent drugs translates to an increased understanding of the importance of the development activities. As quality-by-design approaches prove their worth, we expect this trend to continue well into the future.”

Pandemic impact
Despite the fact that not all vaccines need to be freeze-dried, there is an overall positive impact on the demand for lyophilization happening as a result of the current pandemic situation, highlights Reuter. “Freeze-drying is the best way to safely and quickly achieve a successful formulation and facilitates the transport of pharmaceuticals to warmer regions,” he says. “Whether this is a long-term trend, however, cannot be assessed at this point in time.”

“In the short term, product stability for the COVID-19 vaccines will not be an issue in developed countries with cold supply chain capabilities because doses will likely be administered rapidly after manufacture,” Morbey adds. “However, with the potential for additional waves of the virus and the unknown approval timeline, it will be critical to stockpile both vaccines and therapies in order to have product available to meet future demand. I am quite confident that many vaccines are currently being simultaneously developed as both a liquid and lyophilized dosage form.”

The same principle applies to proven anti-viral products, Morbey asserts. "If the liquid presentation is stable for 12 months but the lyophilized presentation is stable for four years, the current demand does not require more than 12 months of shelf-life," he explains. “However, once the pandemic is under control, shelf life may become prohibitive for maintaining stockpiles to combat new outbreaks. For under-developed countries without cold supply chain capabilities, stable lyophilized vaccine and therapies are needed.”

Sacha remarks on the development of mRNA platforms, which are not necessarily very stable in solution at room temperature. “These platforms may require cold storage that creates challenges for effective distribution around the world,” he states. “There is a potential that lyophilization can simplify the supply chain for these vaccines and facilitate widespread, global vaccination efforts.”

A further impact of COVID-19 is in the form of manufacturing capacity, which is being exhausted, continues Morbey. “Government agencies have acted quickly to buy manufacturing capacity from large contract manufacturers to support mass production of vaccines,” he says. “With reduced liquid manufacturing capacity, drug developers can look to lyophilized presentations as a first step instead of a last resort.”
Trends gaining traction
Two trends are particularly important in Morbey’s opinion to continue gaining traction within the industry—understanding the importance of product-specific lyophilization cycle development, and standardization of lyophilization equipment capabilities, controls, and PAT. “Cycle development is critical to ensure product quality and is dependent on the formulation characteristics and freeze-dryer capabilities,” he notes. “Technologies exist to fully characterize and understand product characteristics and develop cycles appropriately. When cycles are implemented on outdated equipment or poorly controlled equipment, all the development and optimization efforts can be thrown out the window.”

Increasing system complexity, efficiency, and flexibility is a primary trend for Reuter. “As a result, there is an impetus to implement new technologies in the lyophilization system, for example PAT tools—not only for process monitoring but moreover for process control, making the process parameters adjustable within an allowable range,” he says. “Through better process understanding, it is possible to significantly reduce the freeze-drying process duration and in combination with highly flexible fill/finish systems, small batches with rapidly changing container types, formats and ingredients can be processed.”

Another trend highlighted by Sacha is a reduction in the size of the lyophilizer itself so that efficiency can be increased. “Smaller lyophilizers may be needed to accommodate smaller volumes of product,” he states. “Biologic formulations are typically processed in smaller volumes than for many small molecule formulations and the formulations are quite expensive. Operating with smaller equipment will reduce loss of material and may improve handling of the product.”

Replacing currently used refrigerants with more environmentally friendly ones is also a consideration of Reuter. “Furthermore, investigating and implementing alternative heat sources, such as infrared or microwave, may also improve system efficiency and make lyophilization more attractive,” he comments. “For some lyophilized products, continuous manufacturing can be beneficial and spray freeze-drying has a positive future for certain application fields.”

“Manufacturing of lyophilized dosage forms is a tried and true process for organizations with this expertise. Significant changes are not needed; however, continuous improvement of equipment controls, PAT devices, and implementation of process understanding at commercial scale will lead to improvements in lyophilization practices industry wide,” Morbey concludes. “With the right equipment, quality systems, and development expertise, the lyophilization process is a low-risk operation with significant benefits to the product.”

Reference

Manufacturing — Contin. from page 24
amount of residual risk and deal with those potential repercussions in commercial manufacturing, in favour of speedier outcomes. So, it comes down to collaboration and building a strategy together to determine how much time and effort will be spent identifying user, technology, and manufacturing risks. Both parties will need to decide on either a ‘fast’ approach, in which the customer agrees to accept transferring more risk, or a more thorough approach that draws risk down further during design and development, even if that takes more time.

Connected devices
PTE: What are some considerations for designing and manufacturing a drug delivery device that is connected to the Internet?
Conger (Phillips-Medisize): For connected drug delivery devices, you introduce design and manufacturing techniques beyond what are needed for a typical mechanical device. Two additional considerations require significant attention in the design process: validation of the software that goes into the device and managing the cybersecurity of the device.

Validation is typically done against the ISO standard, IEC 62304 (1), which encompasses the process of managing software development through the entire lifecycle, from the beginning of development through the end of the market life of the device. By way of example, development and management processes at Phillips-Medisize conform to this standard, which provides information on how to develop the device, how to document the development, and how to test it and validate the device so that it meets all requirements.

Device cybersecurity requires as much attention as validation. Once a device is connected, the potential for malicious remote device intervention remains a threat. For this reason, the United States Food and Drug Administration (FDA) has issued detailed guidance on how to approach device security, which includes taking a risk-based approach to both the software and hardware of the device (2). Risk assessments should be conducted to determine what could go wrong or where vulnerabilities exist, and then correlated to how serious the consequence is of each identified risk. If it’s determined to be a serious risk, the mitigation required to prevent the risk becomes significant. Whereas, if the potential risk is not very high, the effort to mitigate is much less significant.

References
Streamlining Method Transfer Across Global Sites

New method-transfer kits help simplify analytical method transfer for global site certifications.

Method transfers are required to enable critical medications to reach global markets. Challenges exist due to staggered submission timelines, different health authority requirements (e.g., from FDA [1] in the United States, the European Medicines Agency [EMA] [2] in the European Union, and the Brazilian Health Regulatory Agency [ANVISA] [3]), and varied importation standards and testing requirements. In China [4], Russia [5,6], and Mexico [7], for example, testing on imported medicines must be performed by government agencies or government-approved laboratories. In other cases, the testing must be performed locally in the country involved (e.g., in Brazil, Peru, Chile, Argentina, Korea, and Japan).

Given extended method-transfer timelines, discrete material batches are often used for each site transfer. This practice can lead to duplicated efforts (e.g., in authoring new test protocols and generating new originating laboratory data across multiple methods throughout product lifecycles).

New approaches to analytical method transfer are being evaluated to help streamline the overall transfer and site-certification process. This article examines one solution: standardized method-transfer kits, designed to improve sustainability and consistency for site-to-site comparisons. It also reviews and summarizes global regulatory guidance for analytical method-transfer.

Global guidance

A number of different regulatory guidance documents recommend different approaches to analytical method transfer. In the US, FDA’s guidance [1] on analytical method transfer is part of the agency’s overall guidance on method development, validation, and lifecycle management. For method transfer, FDA recommends performing comparative studies to evaluate accuracy and precision and assessing inter-laboratory variability across originating and receiving laboratories. For stability-indicating methods, both types of sites analyze forced degradation samples, or samples that contain pertinent product-related impurities.

The European Commission, Health and Consumers Directorate-General guidelines [2] outline that a method-transfer protocol should include, but not be limited to, identification of the relevant test method(s) and testing to be performed, standards and samples to be tested, special transport and storage conditions, and acceptance criteria [2].

The acceptance criteria should be consistent with the method validation. They should also align with expectations from the International Council for Harmonization (ICH)/and International Cooperation on Harmonization of Technical Requirements for the Registration of Veterinary Medical Products (VICH).

ANVISA’s guidance outlines regulators’ expectations for the validation of analytical and bioanalytical methods [3]. ANVISA considers a method transfer to be successful as long as it ensures that precision, specificity, and linearity are evaluated.

Adding to the different analytical method-transfer recommendations are guidance documents published by the International Society for Pharmaceutical Engineering (ISPE), the United States Pharmacopeia (USP), and the World Health Organization (WHO). ISPE recommends that, ideally, at least two analysts at each lab independently analyze three lots of product in triplicate; which results in 18 different executions of the assay method [8].

USP’s <1224>, which discusses comparative, co-validation, and revalidation approaches to method-transfer testing, recommends that testing be performed on homogeneous lots of target material [9], while WHO lists possible experimental designs and acceptance criteria for test methods to account for the variability and sensitivity of the method and the specifications for the quality parameter [10].
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Robust strategy needed

Despite differences in site-certification guidance, it is essential that companies develop a robust method-transfer strategy that will consistently generate comparable data across laboratories. From the authors’ experience, as noted in a position paper on transfer of analytical methods (11), a better overall prediction of consistent longer-term method performance is ensured by testing one or two representative and/or range-challenging batch(es) with an increased number of testing setups, rather than performing fewer setups with an increased number of batches. Without advanced planning, sample procurement, protocol authorship, and approval are time consuming and laborious, and can threaten project timelines. Method-transfer kits were designed to contain centrally-managed batch(es) of representative material (inclusive of matrix considerations such as strengths and impurity profiles), and pre-defined and approved protocols to use for method transfers throughout the product lifecycle.

The authors tested the kits. This article describes the process as well as the results that they observed. A method-transfer kit (MTK) includes representative materials to facilitate comparison of method performance across multiple laboratories during the product lifecycle. In addition, an MTK defines the setups, conditions, and acceptance criteria for the given batch across the originating and all receiving laboratories. Per WHO (10), FDA (1), USP <1224> (9), and EMA (2) guidance, protocols are established prior to method transfers and have pre-defined acceptance criteria. Much has been written about the process used to establish acceptance criteria, which is beyond the scope of this article (11–13). Using the MTKs, pre-approved originating and receiving laboratory protocols are associated with and leveraged for the first and future method transfers.

MTK benefits

Once originating laboratory data are generated, the MTK benefits begin to be seen. The originating laboratory data are generated once, and the MTK material stability data are leveraged for multiple transfers within the stability period. For each analytical property, the stability period is defined as the time when the material must be comparable to the first originating laboratory data set. It does not mean that the material simply meets the shelf-life specification. During method transfer, each receiving laboratory will perform the same evaluations on the same material, with the same criteria for comparison to results from the originating laboratory.

MTKs provide more control over sample variability to allow focus on assessment of method performance between originating and receiving laboratories, regardless of when the transfer occurs. MTK samples can be leveraged to enhance the understanding of control strategy at each receiving site as well. For example, incorporation of a representative degraded sample can demonstrate that correct results can be generated both at release and throughout the product lifecycle. When the receiving laboratory analyzes a degraded sample that its staff has never seen before, it affords an opportunity for them to discuss potential impurities and degradation chemistry with subject matter experts using tangible samples. Discussion of the degradation mechanisms, if they are known, can assist with troubleshooting before, during, and after transfer activities.

Establishing a method-transfer kit

Figure 1 outlines the key steps to establish and maintain method transfer kits. First, there must be an understanding of sample numbers

Figure 1. Steps to establish and maintain a method-transfer kit (MTK).
required per kit and the total number of kits required. For a typical small-molecule drug product, the analytical test methods may include those attributes listed in Table I. To determine the sample numbers required, the number of samples required to execute each method should be considered in the broader context of feasibility and method training studies, and the number of independent setups required to demonstrate equivalence or statistical comparability between the originating and all receiving laboratories.

In the hypothetical example outlined in Table I, the number of tablets required to execute a single setup of the method is 20 tablets. However, when performing the method transfer itself, due to multiple replicates for each setup and testing in both the originating and the receiving sites, 140 tablets will ultimately be required for training and six setups at one receiving site. Table I indicates the minimum number of tablets required in this situation. Providing samples for training and transfer activities in a single MTK simplifies shipments and performance tracking, beginning with training and continuing throughout the transfer.

If there are multiple doses, it may be necessary to establish the same number of samples for each dosage strength. Alternatively, a bracketing strategy may be used, in which high- and low-dose strengths are leveraged to qualify the receiving laboratory, provided there is enough confidence in the methods and formulations that mid-range doses behave in a manner similar to high and low doses.

For example, dissolution might have different release profiles for each strength. In this case, a dissolution MTK might be required for the intermediate doses, but an assay or uniformity of dosage units (UDU) test at the middle dose might not be required if working solutions are of comparable concentrations.

Finally, the total number of method transfers that may occur within the projected shelf life of the MTK should be considered. In the hypothetical example in Table I, if 10 method transfers to different sites are projected, at least 4000 tablets should be placed into MTK inventory.

One option involves packaging enough dosage units in a single MTK to satisfy feasibility and site certification for all quality attributes. Another alternative is to tailor the kits based on individual analytical attributes. In the latter case, a kit would be defined to accommodate enough materials to qualify a laboratory on a single attribute.

For example, microbial testing is often performed by a separate laboratory group than that for chemical testing. Separate kits eliminate sharing of materials at the receiving lab (a possible source of cross-contamination).

In another example, an impurities method-transfer kit might contain an impurity-enriched sample in addition to a typical sample that might contain very few, if any, impurities. Alternatively, an in-situ preparation could be provided to force the sample to degrade artificially (e.g., via exposure to acid, base, peroxide, heat, or light). Alternatively, impurities could be provided to spike into the sample, if such an impurities’ mix is not already part of a system suitability mixture. For these cases, the protocol will define the method of preparation, to drive MTK consistency.

Determining the best storage conditions
Stability data generated in early clinical development are leveraged to define representative sample MTK storage conditions, to maintain product integrity and stability in cases where receiving laboratory results are comparable to originating laboratory results. Generally, to provide the greatest long-term stability, more conservative packaging and storage conditions are applied to MTKs. For example, to extend expected shelf life for drug product materials that must be stored at refrigerated temperatures, for MTKs, product might be packaged in glass bottles, placed in a secondary laminated foil liner for additional light/moisture protection, and stored under refrigerated conditions.

For drug products that are normally stored at refrigerated temperatures, frozen or deep-frozen storage can also be considered to enhance product shelf life. For protein pharmaceuticals, it is important to avoid storage at the drug product formulation’s glass transition temperature (14–16). It is also important to avoid thermal cycling, to minimize the formation of impurities during sample handling.

Finally, it has been beneficial to provide acceptable short-term alternate storage conditions on the MTK label based upon existing material stability knowledge (e.g., acceptable

<table>
<thead>
<tr>
<th>Analytical attribute</th>
<th>Number of samples required per execution of the method</th>
<th>Number of samples required for method feasibility</th>
<th>Number of samples required for method transfer per site</th>
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</tr>
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<td>Assay/uniformity of dosage units</td>
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<td>120</td>
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<td>Impurities</td>
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<td>5</td>
<td>30</td>
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<tr>
<td>Dissolution</td>
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</tr>
<tr>
<td>Water</td>
<td>5</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>Microbial testing</td>
<td>120 (depends on tablet mass)</td>
<td>Not applicable</td>
<td>120</td>
</tr>
<tr>
<td>Total (minimum for transfer and feasibility)</td>
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</table>
storage of transfer kits for up to one month at ambient conditions during transfer for drug products that are stable and normally stored at ambient conditions. Such label information can ease the laboratory operation and address compliance considerations when handling such MTK samples.

**Kits for large molecules or less stable materials**

Special considerations are required for materials that change during routine storage (e.g., large molecules, peptides, inherently unstable small molecules) when more conservative storage conditions are not possible. The degradation rate itself, depending upon severity, could pose problems when comparing mean results for method transfer and could be so severe that the MTK approach may not add value without alternative comparison options.

In the case of a refrigerated complex biologic that may be stored at more conservative conditions, the specification may allow for an end-of-shelf life specification that permits substantial degradation while still maintaining efficacy. In the case of a refrigerated complex biologic that may be stored at more conservative conditions, the specification may allow for an end-of-shelf life specification that permits a change in the molecule’s heterogeneity while still maintaining its efficacy. In this scenario, the receiving laboratory may demonstrate that its staff can accurately quantitate relevant analytical properties (e.g., assay and impurity for small-molecule drug products or charge heterogeneity for complex biologics) on a sample that has degraded near the specification limit in order to demonstrate capability.

Method transfers using MTKs

Once MTK materials have been established in the appropriate quantities, and stored in a manner that ensures their stability, method-transfer activities can begin. Minimal benefit will be realized from the first method transfer (see Figure 2a); however, subsequent transfers show that central storage and distribution of representative materials is very efficient.

In collaboration with the team’s statistician, the analytical chemist working on the method transfer generates protocols that establish the experimental plan, along with the acceptance criteria. MTKs are then provided to both originating and receiving laboratories so that the receiving laboratory can begin feasibility studies while the originating laboratory executes the official transfer activities. The receiving laboratory can execute the official transfer after the feasibility studies have been completed and reviewed by the originating laboratory. After both laboratories complete the experiments, analyze and review the data, and write the final transfer report, the real MTK benefits will be seen in the second and later transfers (see Figure 2b). For each subsequent transfer that utilizes the same MTK, the method-transfer process becomes more streamlined.

**Maintenance of the MTKs**

While storage conditions for the MTKs are intended to provide extended stability, the materials should be reevaluated periodically to confirm continued stability and suitability for use. Initial re-evaluation dating may be defined based upon existing stability data. For example, three-year development data under long-term conditions in addition to accelerated stability and/or other stressed conditions might be used to justify at least an initial three-year re-evaluation period. Risk-based predictive stability models could also be considered to assess overall stability and propose initial re-evaluation dating requirements.
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Knowledge management

At the end of the re-evaluation period, expanded product stability knowledge management can be utilized to justify accepting the originating data package without change for an extended stability period. If an appropriate data set does not exist, the MTK material will be re-evaluated by the originating laboratory using stability-indicating methods. Re-evaluation tests depend on registered product analytical properties as well as properties that have potential to change over time.

For small-molecule solid oral dosage forms, potency is consistently included in re-evaluation plans. Other tests depend on historical product trends and may include water, purity, dissolution, or other properties that have been demonstrated to have potential to change on stability.

For complex biologics such as monoclonal antibodies, biopotency, monomer purity by size exclusion chromatography, charge heterogeneity, reduced and non-reduced purity by capillary electrophoresis sodium dodecyl sulphate, and critical excipients are consistently included in re-evaluation plans.

Successful re-evaluation test results can result in a decision to extend the dating for MTK material. MTK material with an undesirable change can result in the need to retire the material. Documentation is necessary as part of re-evaluation planning. Documents should be saved in a format that is controlled with revision history. In accordance with ICH Q7 (17), as additional information is learned about the product, the re-evaluation strategy may be revised to extend or reduce dating and to add or remove characterization tests.

Case studies

In the authors’ experience, MTKs have allowed transfer time to be reduced from just over two months to approximately one month (per method). Additionally, when using MTKs, the benefits of avoiding the need to continually identify suitable transfer samples, generate meaningful acceptance criteria, and complete thorough protocol reviews cannot be overstated. Furthermore, MTKs stored in a central location, staffed with professionals who have an in-depth knowledge of import/export compliance requirements, can be shipped efficiently to speed transfer initiation.

For the first small-molecule MTK, tablet kits were shipped to seven locations in Europe, Asia, North America, and South America. Speciality microbial MTKs were supplied twice for microbial method verifications. Because a single batch of material was supplied to last for an extended time period, method performance comparisons could easily be made across different times, high-pressure liquid chromatography (HPLC) columns, mobile-phase batches, media, instrument types, capillaries, cartridges, and labs to determine assay consistency or variability for each method or property. In addition, results from certifications across sites may aid in proactively preventing bias or reducing method variability.

The originating site data set was powered with additional testing (n=8 setups in duplicate versus n=6 setups in duplicate for all receiving labs) to better capture anticipated method variability for method-transfer assessments. Originating laboratory data, along with method validation accuracy and precision data, were used to establish acceptance criteria for the transfers.

Results showed no statistically significant difference between the originating laboratory and each of seven receiving sites over a three-year period. These data demonstrate that both the overall average results and the setup variability for each laboratory were in alignment with the originating laboratory data package, and each receiving laboratory was successfully certified through analysis of the same MTK materials over a three-year period (Figure 3). In a second small-molecule MTK example, assay results demonstrated no statistically significant difference between the originating laboratory and each of four receiving sites (Figure 4).

While Site 3 met all acceptance criteria, the laboratory had higher variability and a lower average than observed at all other sites. This did not happen with the first example, suggesting that it might be a good idea to review site implementation experiences a bit more closely in order to identify sources of variability, such as those from sample preparation, and to monitor post-transfer data more closely.

In conclusion, a systematic approach was outlined to select, store, and distribute representative material and
Pharmacovigilance Under Scrutiny: Why Companies are Falling Short

Despite pharmacovigilance legislation being in place for nearly a decade, many companies are still struggling to fulfil obligations.

Vanessa Fachada Oliveira is a pharmacovigilance manager and EU QPPV at Arriello.

It is now eight years since current European Union pharmacovigilance (PV) legislation came into force in Europe (1), requiring that pharmaceutical companies targeting the region must put in place a number of formal measures to monitor the safety of products and any issues once products are being consumed in the real world. The measures also mandate that life-sciences companies must run, check, and document their PV activities, so that regulating authorities can be confident that standards are being upheld and that nothing is being missed.

To this end, pharmaceutical organizations must be able to provide evidence of strong standard operating procedures—on demand. Yet, even today, a majority of companies are still struggling to fulfil their obligations, potentially causing marketing authorization holders (MAHs) to fail inspections, incur fines, and see products withdrawn from markets. One of the reasons for common failings in PV process documentation is that the EU has not set out clear guidelines about how or where companies should go about this, which leaves too much room for interpretation and for potential gaps in provision. The following are 10 ways companies are commonly going wrong and what they can do now to reduce ongoing risk.

Quality management system inadequacies

The 2012 EU PV legislation makes clear that quality systems should form an integral part of an organization’s PV system. But although other strong standard operating procedures (SOPs) may have been documented as part of general quality systems, there is often nothing relating specifically to PV. That is, there is no specific information about what is required in terms of procedures for managing deviations, for instance, for what happens if a new qualified person responsible for pharmacovigilance (QPPV) is appointed; for how external service partners are qualified; or for what the business continuity plan is and how this is tested, and so on.

These omissions can result in inadequate integrity and management of pharmacovigilance data, difficulty identifying and implementing corrective actions and preventative actions (CAPAs), and incomplete oversight/compliance management of a PV service provider.

Gaps in training, or associated reporting

Training-related failures can occur because it is not obvious who is responsible for or who actually needs PV training. Depending on the organization, the remit for organizing training could fall to the human resources (HR) department, the quality department leadership, or the PV function itself. What’s less obvious is that everyone in the company will need PV training—from the most senior managers to manufacturing teams. That’s because anyone could find themselves the recipient of safety feedback, which means everyone needs to know what action to take next—and how quickly.

To ensure that no training needs are missed, there should be a clear training plan, and formal records showing which employees have attended which sessions and when. The QPPV in particular must attend regular training and have up-to-date certificates.

Quality people who perform audits must have at least some PV training too, yet this is often found not to be the case.

Breaks in supply-chain continuity

Manufacturers as well as MAHs and distributors could find themselves the first port of call for a safety report. A safety data exchange agreement should set out the respective PV responsibilities of each party, who the QPPV is, who will manage actions relating to adverse reactions, and associated reporting. For a distributor, the obligation might simply be to forward all relevant information to the MAH—unless that company also has a remit for local PV activities.

Lesser failings, but nonetheless important to put right, include the omission of special situation reports, and provision for archiving, retention periods, and exchange of information.
EU pharmacovigilance legislation

European Union pharmacovigilance legislation, which came into effect in July 2012, was the biggest change to the regulation of human medicines in the region since 1995. It had significant implications for applicants and holders of EU marketing authorizations, as well as for patients, healthcare professionals, and regulators.

The development of the pharmacovigilance legislation was based on the observation that adverse drug reactions (ADRs), 'noxious and unintended' responses to a medicine, caused around 197,000 deaths per year in the EU. As a result, the European Commission began a review of the European system of safety monitoring including sponsoring an independent study, as well as extensive public consultation through 2006 and 2007.

This process resulted in the adoption of a Directive and Regulation by the European Parliament and Council of Ministers in December 2010, bringing about significant changes in the safety monitoring of medicines across the EU (1). The legislation amended existing pharmacovigilance laws and was accompanied by the implementing regulation (2), a legally binding act published by the European Commission in June 2012 that provides details on the operational aspects for the legislation.

In October 2012, the pharmacovigilance legislation was amended once more, to further strengthen the protection of patient health by allowing prompt notification and assessment of safety issues (3).

Practical measures to facilitate the performance of pharmacovigilance in accordance with the legislation are available in EU guidance on good pharmacovigilance practices (GVP) (4).

The legislation affects marketing authorization applicants and holders in the following ways, aiming to clarify their roles and responsibilities, minimize duplication of effort, free up resources by rationalizing and simplifying reporting on safety issues, and establish a clear legal framework for post-authorization monitoring.

References
2. EMA, Commission Implementing Regulation (EU) No. 520/2012 (Brussels, June 2012).

— Vanessa Fachada Oliveira, pharmacovigilance manager and EU QPPV, Arriello

Followings with the PSMF

The pharmacovigilance system master file (PSMF) is one of the main documents of the company’s PV system. It should provide a very clear overview of all critical PV processes and procedures for managing adverse events and safety signals; the key stakeholders; full details of the QPPV and their experience and contact details; documentation showing how the organization will manage compliance with the legal requirements; and key performance indicators (KPIs) and the rationale behind these.

The PSMF must be kept up-to-date at all times, so there must be a process for ad-hoc revisions as well as periodic updates. If the competent authority asks to see a copy of the file, the company must be able to deliver a fully updated document within seven days. Failings can be for something as simple as poor formatting or omitting an index to allow easy navigation. If the PSMF preparation is subcontracted, another oversight inviting a penalty might be the lack of MAH involvement in any document revisions.

Inadequate QPPV oversight

If the qualified PV person—who carries personal liability for PV failings, in addition to any company penalties—does not have sufficient oversight of the process for safety variations preparation, submission, and implementation, or over KPIs and adverse event reporting, this could also result in a failed inspection and potential fine.

Insufficient attention to risk management

This is one of the topics with the largest number of critical findings over time during inspections and includes findings related to poor maintenance of product information (routine risk management) or to implement additional risk minimization measures (aRMM), such as educational materials or pregnancy prevention programmes.

Failure to consistently collect and manage safety information

Often the breakdown here is a failure to identify and track all potential sources of spontaneous safety data or to reconcile adverse event monitoring activity with medical information and product quality complaints. This breakdown can lead to safety signals being missed. Failing to properly validate the database for individual case safety report (ICSR) management can also lead to a fine, especially for small-to-medium enterprises (SMEs), which can't justify the cost of a top-of-the-range PV database.

Using spreadsheets or other tables to manage validation is not acceptable, but there are affordable options to formalize activity here. Failure to transfer safety data from previous MAHs during an acquisition can also catch companies out.

Ongoing gaps in safety evaluation

These gaps concern benefit-risk and signal management and aggregate
reports (PSURs). Common mistakes include inaccurate sales and patient exposure figures; the inclusion of unrelated adverse event reports; failure to include relevant cases in the benefit-risk analyses; and late updating of product information. Other issues include failure to discuss all sources of potential signals; and a lack of rationale for the report frequency.

Poor links between departments or with third parties
It’s important to include teams monitoring MAH websites for comments/safety reporting and to keep tabs on any general company email addresses that people might use to report safety data.

Failures in business continuity provision
This issue includes validating controls over access to sensitive patient medical information and, if fireproof/ waterproof filing cabinets have been swapped for digital archiving, that such systems meet all required parameters.

Tightening control
With so many factors to get right in the way of systematic information capture and reporting, it is unsurprising that PV departments are getting some of this wrong and are feeling overwhelmed by the responsibility.

One way to alleviate immediate concerns is to pursue unbiased feedback on current provisions from professionals with experience of a diverse range of approaches and systems. They will be able to bring to bear the latest best practice, based on the effective ways other companies are tackling this—or perform a gap analysis that can help target remedial action.

In due course, the EU should clarify and update its guidance, so pharma companies will be better able to understand what they need to aim for. It’s important not to wait until then, however. Competent authorities are starting to perform remote inspections now, which is likely to lead to increased coverage and frequency of these spot-checks as more auditor capacity is freed up.

Reference
1. EMA, Commission Implementing Regulation (EU) No. 520/2012 (Brussels, June 2012), PTE

Figure 4. Example method-transfer kit results from the originating laboratory and four different receiving sites.
Determining Water Content with a Novel Karl Fischer Titration Approach

A new approach to testing water content in biologics is needed that will give a more accurate determination of actual water content in the biologic.

When developing and validating new water content determination methods for pharmaceutical materials, the need for an oven extraction is often necessary when the material has dissolution issues during titration (1). During these validations, it is common to spike sample material with standards in order to obtain a linearity curve for the method. Current commercially available solid standards are certified for analysis to a minimum temperature of 140 °C, which is acceptable for most materials (2); however, biologic materials often degrade at temperatures below the current commercial standards (2). This study evaluated the application of glucose monohydrate (GlcH) as a standard. The thermal properties of GlcH (3) make it an excellent candidate because it is a saccharide, which is a common cryoprotectant for biological materials (4–6), and thus should be compatible with a multitude of samples. GlcH was not spiked into sample material and, instead, was analyzed as received. This was done because of limited access to sample material.

Material and methods

Materials
GlcH was sourced from a bulk supplier with a water content value of 9.0% per the accompanying certificate of analysis (CoA). All calculations of percent recovery for the bulk GlcH material were calculated from the CoA value. All preparations of GlcH were performed under ambient laboratory conditions. Bulk sample material for GlcH was stored in a desiccator when not in use to minimize moisture adsorption over time. Glucose in the absence of a hydrate will be identified as Glc.

Instrumentation
- KF headspace oven—a KF headspace oven was used that had an operating temperature range of 50 °C to 250 °C and a 32-vial autosampler.

Methodology

Initial evaluation of the thermal properties of GlcH was performed through use of a temperature gradient using the KF headspace oven. For this analysis, the temperature was ramped from 50 °C to 150 °C at a rate of 1 °C/minute with a nitrogen flow rate of 50 mL/minute. The upper temperature limit of 150 °C was chosen since the GlcH was expected to degrade at this point by undergoing a Maillard reaction, which would create excess water (7). The results from the temperature gradient, shown in Figure 1, demonstrate the drift and the micrograms of water measured towards the asymptote to approach a slope of zero just below the temperature of 70 °C. This matches the expected value from literature and is believed to be the temperature at which the hydrogen bond between glucose and the water of hydration breaks, which releases water from the GlcH (8).

The GlcH was analyzed using the KF headspace oven at varied temperatures, as outlined in Table I, and the percent water measured was evaluated against the certificate of analysis value of 9.0% water as the percent recovery. The percent recovery results from Table I suggest GlcH does not release water as readily as the temperature gradient analysis in Figure 1 indicates.

Further evaluation of the GlcH was performed using thermogravimetric analysis (TGA) to determine the rate at which water is released. The GlcH was analyzed at two different temperature ramp rates, 1 °C/minute and 10 °C/minute, to evaluate the differences between the sample slowly coming to temperature and the sample rapidly coming to temperature (i.e., the sample being
Discover Functional Film Coating Formulations for an Easy and Fast Coating Process of SODFs

ON-DEMAND WEBCAST
Aired: Wednesday, September 16, 2020

Register for this free webcast at:
www.pharmtech.com/pt_p/discover

Event Overview
Functional film coatings can be applied to solid oral dosage form (SODF) drugs to mask taste or odor, provide a moisture barrier, offer enteric protection, or modify the release of the drug.

This webcast will review several formulation examples, case studies, and how film coatings are applied and processed. The application of ready-to-use film coatings will be explained.

Learn which formulation can be used for reliable odor and taste masking or how the dissolution profile of an API tablet can be modified. In addition, the properties of different coating formulations will be investigated.

Key Learning Objectives
• Understand the function of polymers for taste and odor masking, moisture barriers, enteric protection, modified release
• Learn how hygroscopic tablet cores can be protected
• Discover the benefits of ready-to-use film coating formulations

Who Should Attend
• Research & development people, process engineers, technicians in the field of solid dosage forms for dietary supplements and pharmaceutical industry.

Presenter
Abderraouf Allia
Business Development Manager
BIOGRUND

Moderator
Rita Peters
Editorial Director
Pharmaceutical Technology

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analyzed is inserted in a preheated oven) (9). The thermograms, as shown in Figure 2, show the rate at which GlcH is heated can greatly affect the behaviour of the material and how the moisture is released. One potential and critical explanation for this difference is that GlcH undergoes a phase transition at 83 °C that causes the structure to re-arrange, which entraps the bound water within the material. The phase transition of GlcH has been extensively evaluated (3) and explains the various mechanisms that caused the differences in the release of water. As shown in Figure 1 and Figure 2, both analyses took place under nitrogen flow and were uniformly heated at a rate of 1 °C/min, and GlcH appears to effloresce just below 70 °C. In order to increase the heating rate of GlcH to be more uniform, the particle–particle interaction and, in turn, the packing coefficient, would need to be increased to optimize the heat transfer (10). An aliquot portion of the GlcH was put through a ball mill for five minutes to reduce the particle size in order to better optimize the packing coefficient and subsequent heat transfer of the material. The quantitative reduction in particle size was not evaluated; however, increased duration in milling time would likely further decrease the average particle size, thus increasing the packing coefficient (11). The ball-milled GlcH was then analyzed on the TGA at a ramp rate of 10 °C/min. Figure 3 shows the thermogram from the ball-milled GlcH overlaid with the thermogram from the 1 °C/min-ramp-rate analysis of bulk GlcH. The thermograms from the ball-milled GlcH more closely matched the thermogram of the 1 °C/min-ramp-rate analysis of bulk GlcH.

Table I. Initial analysis of glucose monohydrate (GlcH) at various temperatures.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Temp (°C)</th>
<th>% Water</th>
<th>Percent recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk GlcH</td>
<td>70</td>
<td>7.26</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.08</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>7.39</td>
<td>82</td>
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<td></td>
<td>80</td>
<td>7.91</td>
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</tr>
<tr>
<td></td>
<td>100</td>
<td>8.13</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.00</td>
<td>89</td>
</tr>
</tbody>
</table>

Figure 1. Temperature gradient from Karl Fischer oven titration.

Figure 2. Thermogravimetric analyzer analysis of glucose monohydrate at varied ramp rates.
Pharmaceutical Technology Europe

Operations

to determine the percent recovery. During sample preparation it was noted the GlcH was difficult to handle because milling the material caused it to become statically charged. Weighing a specific sample size and ensuring proper sampling was difficult since the GlcH stuck to the sampling utensils and the walls of the glass vial in which it was stored. To alleviate this, the flow aid, lauric acid, was added to minimize the sticking of the milled GlcH to various surfaces (3) (10). Lauric acid was added in various concentrations to evaluate its impact on the measurement consistency of GlcH water content analysis and the results are reported in Table II as well as the prepared concentrations.

Conclusion
GlcH is an acceptable standard for use in water content determination using a KF headspace oven at temperatures below 100 °C. This would bridge a gap since there are no current standards available for use at temperatures below 140 °C and would allow extension of KF headspace oven analysis to materials that release water at or below 100 °C. The reduction in particle size was a key factor in ensuring consistent measurements and will likely need further evaluation to determine the ideal grain size for ideal testing parameters. The use of a flow aid such as lauric acid is recommended to ensure sampling, and preparation of the material should be consistent to improve sample precision. The use of alternative flow aids may be applicable but would need further evaluation.

References
5. C. J. Capicciotti et al., ACS Omega 1 (4) 656-662 (2016).

Table II. Initial analysis of glucose monohydrate at various temperatures.

<table>
<thead>
<tr>
<th>Sample preparation</th>
<th>Temperature (°C)</th>
<th>Percent water (%)</th>
<th>Percent recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ball milled glucose monohydrate</td>
<td>130</td>
<td>8.59</td>
<td>8.60</td>
</tr>
<tr>
<td>130 Average</td>
<td>8.60</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>8.57</td>
<td>99.7</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>8.64</td>
<td>100.5</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>8.65</td>
<td>100.6</td>
<td></td>
</tr>
<tr>
<td>63 Average</td>
<td>8.60</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Ball milled 1% lauric acid: glucose monohydrate</td>
<td>130</td>
<td>8.59</td>
<td>8.54</td>
</tr>
<tr>
<td>130 Average</td>
<td>8.57</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>8.45</td>
<td>98.7</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>8.43</td>
<td>98.5</td>
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<td>70</td>
<td>8.52</td>
<td>99.4</td>
<td></td>
</tr>
<tr>
<td>63 Average</td>
<td>8.50</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Ball milled 10% lauric acid: glucose monohydrate</td>
<td>130</td>
<td>8.02</td>
<td>100.0</td>
</tr>
<tr>
<td>90</td>
<td>7.98</td>
<td>99.5</td>
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</tr>
<tr>
<td>80</td>
<td>7.96</td>
<td>99.2</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>7.95</td>
<td>99.1</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Thermogravimetric analyzer analysis of glucose monohydrate milled compared to non-milled.
Viatel™ Bioresorbable Polymers

Bioresorbable polymers provide formulation scientists the opportunity to design better drug delivery systems, which can lead to improved efficacy, fewer side effects, higher compliance, and ultimately better patient outcomes. Ashland offers five families of bioresorbable polymers for parenteral controlled-release drug delivery systems and medical devices.

For drug delivery, Ashland offers amorphous homopolymers and copolymers, including:
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- Poly(L-lactide-co-ε-caprolactone) (PLCL).

The primary benefit of bioresorbable polymers is they break down via hydrolytic degradation into the monomer components lactic and glycolic acid—both of which are resorbed by the body. A key feature of Viatel™ bioresorbable polymers is that they contain no detectable residual solvents. Additionally, all Ashland Viatel™ bioresorbable polymers meet typical drug and device regulatory thresholds for tin catalyst levels established by health authorities.

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- Guanidine Thiocyanate, GMP
- HEPES Free Acid, GMP
- HEPES Sodium, GMP
- HCl in IPA (6N), GMP
- L-Cystine Dihydrochloride, GMP
- MES Monohydrate—GMP
- MOPS Free Acid, GMP
- Potassium Bromide (KBr)—GMP and API Grade
- Sodium Chloride 5N, Sterile Filtered, WFI Excipient Grade
- Sodium Decanoate, GMP, Functional Excipient
- Sodium Hydroxide 10N, GMP, <5 ppm Cl, made with WFI, BET Tested
- Sodium Hydroxide Solutions, GMP, made with WFI, Low Chloride
- Sucrose—Excipient Grade
- Trehalose—Excipient Grade
- Tris HCl, GMP
- Tris/Tromethamine, GMP, and API Grades
- Uracil, GMP
- Urea, GMP, and API Grade

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E-mail: solutions@catalent.com
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**Injection vials for vaccines for protection against Covid-19**

The vaccines under development to protect against Covid-19 are, like many other drugs, filled in so-called injection or vials made of type 1 borosilicate glass, also known as vials. The large worldwide demand for vials is met by the Gerresheimer Group’s plants in Europe, America and Asia, where they are manufactured to high quality standards for customers in the pharmaceutical industry. The Company has already received initial orders for vials for drugs and vaccines against Covid-19.

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In addition to glass ampoules, injection or piercing vials are the standard for the primary packaging of parenterally administered drugs and vaccines. They are the classic packaging material for numerous vaccines and medicines. Gerresheimer produces the vials in all sizes in accordance with international standards and the requirements of pharmacopoeias.

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Shimadzu was founded in 1875 in Kyoto, Japan, and over 50 years the European Headquarter is located in Duisburg, Germany. The company’s systems and solutions 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. 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.

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

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Partnering for Inhaled Drug Success

Progressing inhaled products quickly to the clinic whilst managing costs, risk and maximising the probability of success are key challenges in any inhaled development programme.

Vectura offers comprehensive services from the pre-clinical stage of development, when customers are looking to overcome complex inhaled formulation challenges, select a delivery device and accelerate development.

With expertise in powder and liquid formulations, as well as a portfolio of proprietary device and formulation technologies, Vectura can help customers developing inhaled drug products for small molecules, biologics or complex combinations.

In early development, selecting a unit-dose capsule or blister device, or a nebuliser may offer benefits in terms of speed and cost. A multi-dose dry powder inhaler (DPI), pressurised metered dose inhaler (pMDI) or nebuliser may be required as a commercial-ready platform to support a later-phase programme. Taking a phase-appropriate decision on the delivery platform for each development stage can reduce costs and risks.

Vectura has expertise across a range of delivery technology platforms, including unit-dose and multi-unit dose DPIs, pMDIs and smart nebulisers, suitable for home or hospital applications. This allows a “device agnostic” approach to best meet the needs of the customer, the development programme and, ultimately, the patient.

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Website: https://www.vectura.com
Cart2Core® - Aseptic Cart Transferring System

Veltek Associates, Inc. has developed an innovative product that nearly eliminates the problematic issue of correct aseptic cart transference. Current industry practice for cleaning and disinfection of the upper portions of the cart, while labor intensive, are manageable. However, cleaning of bases, wheels, casters, and underneath the cart are virtually impossible, can cause numerous problems, and complicate worker safety.

The Cart2Core®, Aseptic Cart Transferring System, provides the ability for cleanroom operations to transfer materials through classified areas while reducing the possibility of cross-contamination. The cart top is able to be transferred to another previously cleaned cart base located in the next classified area. Simply lift the handle and slide the top of the cart onto the next base, leaving the potential contamination behind.

Veltek Associates, Inc.
Available cart configurations include standard carts and custom carts. All carts are autoclavable, sterilizable, chemical resistant, have the capability to be RFID coded, and are constructed of 316L Stainless Steel.

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Computer Systems Validation an (Un-)Manageable Task?

An assessment can identify the critical systems and the gaps in compliance based on intended use, says Siegfried Schmitt, vice president technical, Parexel.

Q. We recently performed a detailed assessment of our computer systems for compliance with the applicable regulations, especially US 21 Code of Federal Regulations Part 11 (1). The aim was to remedy critical systems first, if any gaps were found. However, almost all systems ended up in the critical category and many of these have compliance gaps. We do not have the resources to address all of these now, so how can we prioritize?

A. Your approach to perform a review and apply a risk assessment (RA) is commendable and correct. As you did not provide details about the criteria in your RA and how you weigh them, my answer has to be generic as this is a common issue when it comes to computer systems.

The principles of computer systems validation (CSV) are not dissimilar to process validation. To validate a process, you need to have qualified equipment. Similarly, for CSV, you need to have a qualified infrastructure. Once this is in place, you can then validate software for business purposes. This allows you to focus your compliance assessment on the software.

The next step is to perform a straightforward triage (see Figure 1).

Next comes the risk assessment, and in order to do this logically and compliant, we should follow regulatory guidance. US Food and Drug Administration (FDA) guidance states, “The extent of validation studies should be commensurate with the risk posed by the automated system” (2). Guidance from the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom states, “Validation effort increases with complexity and risk (determined by software functionality, configuration, the opportunity for user intervention and data lifecycle considerations)” (3). The key word here is complexity. When you look through your inventory of computerized systems, you should be able to at least make a distinction between simple and complex systems, such as a Karl Fischer titrator and a chromatography data management system.

The regulations demand that your validation is for the intended use of the computerized system. The intended use should be documented or referenced in the system inventory. All too often, companies fail to document the intended (i.e., actual) use of the system. For example, an electronic quality management system may have many modules, but you may only be using the documentation management and the training module. When you assess your system for compliance, make sure that you assess these modules specifically, instead of a whole range of installed, yet not used, modules. Now you should have been able to identify the critical systems and the gaps in compliance based on intended use. It is generally possible to categorize the remediation effort for eliminating these gaps into short-, medium-, and long-term activities. A short-term solution may be to stop using a particular instrument; a medium-term solution may be an upgrade of the software or a revalidation exercise; and a long-term measure could be the replacement of a piece of automated equipment.

Coming back to your question, you may want to review your approach to assessing your systems and verify you really understand each item’s intended use based on the above recommendations. This should leave you with a much more manageable task in hand.

References
1. CFR Title 21 Part 11 Electronic Records; Electronic Signatures.
2. FDA, Data Integrity and Compliance with Drug CGMP, Questions and Answers, Guidance for Industry (CDER, CBER, December 2018).
3. MHRA, ‘GXP’ Data Integrity Guidance and Definitions (MHRA, March 2018). PTE

Figure 1. Simple compliance assessment for automated systems.
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