The Value of Connected Drug Delivery

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Are We All In This Together?

Rita C. Peters

Achieving herd immunity will require testing, data, a vaccine, and public support.

Through May 2020, more than 100,000 deaths in the United States were attributed to COVID-19; there were more than 350,000 deaths globally. Amid the swirl of news and developments in the past three months, a great deal of information—and misinformation—has circulated the disease and options to combat it.

The COVID-19 pandemic has introduced new terminology and concepts to the public and highlighted the need for refresher courses on good hygiene. Well-established public health practices, such as staying home if you were sick and washing your hands with soap and water for 20 seconds, had to be driven home through public education programs.

Other recommended practices, which some perceived as infringing on personal choice, were met with more resistance and less compliance. Demonstrators have protested the closure of public spaces and businesses. Some people do not understand—or are not adhering to—the concept of social distancing. And, the recommendation to wear a facemask in public has become a political flashpoint.

Public health officials and healthcare providers have had a difficult task communicating about and getting the public to adhere to practices to help control the spread of the virus. The more complex a topic is the more difficult it can be to gain public acceptance and adherence.

If bio/pharma makes a vaccine …

Effective vaccines and therapies are seen as a pathway to return to life as it was before the pandemic. In the past three months, many “promising” therapies and vaccines were heralded in press announcements, often with limited supporting data.

Operation Warp Speed—the name of the Trump Administration’s program to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics—announced lofty goals of producing hundreds of millions of doses of vaccine by the end of 2020.

Will patients take it?

Many experts do not believe that an effective, approved vaccine that provides at least some protection will be available in less than one year. And, concern that the rush to get a vaccine to market will compromise safety may work against efforts to build herd immunity among the population.

Herd or community immunity occurs when a sufficient percentage of the population is immune to a virus because enough people recovered from the illness or were vaccinated. Absent a vaccine, most nations went into lockdown.

Sweden adopted any alternative approach: build herd immunity among its younger, less at-risk population, while leaving most businesses and public spaces open. As of late May, the nation’s immunity rate was expected to be well below projections, while the death rate per capita was significantly higher than surrounding countries (1).

Epidemiologists estimate that 70% or more of the population must be immune to the novel coronavirus to achieve herd immunity. The portion of the US population that has immunity is unknown due to issues with inaccurate and limited testing and reporting (2).

The Centers for Disease Control reports that less than half of the adults in the US get an annual influenza vaccine (3), an indication that the entire population may not line up voluntarily to get vaccinated. Achieving herd immunity will require health officials to educate a wary and confused public of the science-based merits of a vaccine, a more difficult task than getting people to wash their hands.

References
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Generic Drugs in Spotlight as Pandemic Creates Shortages

Jill Wechsler

FDA and the US Congress support innovation and access to cheaper medicines.

The recent surge in demand for certain common medicines hyped as potential COVID-19 therapies led to serious drug shortages at hospitals and pharmacies, notably for the common malaria treatment hydroxychloroquine and antibiotics such as azithromycin. Widespread use of ventilators to relieve respiratory distress in very ill patients, moreover, depleted supplies of sedatives and painkillers administered with such equipment.

These supply problems highlight the reliance of the US healthcare system on generic drugs, many produced overseas or made with imported APIs. Manufacturers have rushed to fill the gaps, particularly to aid patients already relying on these medicines to treat serious medical conditions.

FDA issued guidances on developing more ANDAs in one review cycle by encouraging manufacturers to file more complete applications that avoid time-consuming discussions on application shortcomings.

FDA also seeks to advance the development and approval of more complex generics, such as topicals and inhaled products, as outlined in the agency’s Drug Competition Action Plan of 2017 for facilitating access to less expensive alternatives to a broader range of innovative therapies. FDA has published lists of more than 500 drugs that lack competition and warrant extra agency assistance in determining what tests and data are needed to gain market approval.

Legislative support

Congress also has furthered generic-drug development in approving the long-debated CREATES Act in December 2019 as part of a must-pass budget bill. The measure helps generic-drug makers access innovator supplies needed for bioequivalence testing and product approval, even when the brand is subject to a risk evaluation and mitigation strategy (REMS). The legislation also provides flexibility in establishing shared REMS programs for innovators and generics, another effort to avoid roadblocks to accessing less costly prescription drugs.

To further identify and prevent looming drug shortages, moreover, the legislators also included a provision in the CARES Act, the $2-trillion COVID emergency bill enacted in March that supports FDA efforts to monitor medical product supply chains and ensure access to both drugs and APIs imported from abroad. The bill expands FDA authority to require information on where problems might interrupt access to APIs, as well as drugs, and calls on firms to establish back-up plans for ensuring supplies of critical products.
Generic-drug development also may advance from global agreement on standards for testing and regulating these medicines. A new project of the International Council for Harmonization (ICH) aims to establish bioequivalence standards for immediate-release solid oral dosage forms to support generic product development and approval in multiple regions (8). Additional ICH guidelines for generics are expected, as the group explores opportunities for standards related to a number of complex generic medicines.

These and other initiatives were discussed at an FDA Generic Drugs Forum, which attracted more than 4000 registrants from 73 countries to the online program held April 15–16, 2020. FDA staff provided practical advice to manufacturers on minimizing deficiencies in applications and described opportunities for OGD assistance in developing complex generic products and on navigating the regulatory process (9).

References
9. FDA/SBIA, Generic Drugs Forum, online (April 15–16, 2020). PT

Conducting bioequivalence studies during the current health emergency

To continue the development and testing of new generic drugs during the COVID-19 pandemic, FDA issued a statement (1) providing flexibility to manufacturers encountering difficulties in conducting bioequivalence studies to support new abbreviated drug applications. Similar to the agency’s approach for sponsors conducting clinical trials during the current health emergency, FDA recognizes the potential for quarantines, site closures, travel limitations, and supply chain disruptions to require protocol revisions and changes in plans for information collection. The agency advises on the need to protect study participants overall and to consult with agency staff on issues related to interrupted studies or anticipated changes in research programs.

Reference

—Jill Wechsler
Better Connected: The Value of Connected Drug Delivery

Felicity Thomas

Connected delivery solutions can provide value to industry and patients, through improved medication adherence and outcome optimization.

As the world becomes more heavily reliant on connected devices, it is little wonder that the connected drug delivery devices market is set to witness significant growth in the coming years. According to market research, the sector is expected to grow at a compound annual rate of 35.4% in the forecast period of 2019–2026 (1). Suggested drivers of this projected market growth include a rise in the number of patients suffering with chronic diseases globally, increasing emphasis on preventive care, a general shift towards connected devices rather than manual ones, and improved procedural outcomes offered through connectivity (1).

Delivering drugs through connected devices, such as auto-injectors, smart inhalers, and closed-loop solutions, has been documented as a potential way of improving patient adherence and reducing dosing errors, particularly in the home setting (2–5). “It is widely recognized that the effectiveness of drug delivery devices can be compromised by adherence and patient use error, the likelihood of which are impacted by numerous factors,” confirms Andreas Meliniotis, director, device development, Vectura. “Tracking and reporting use via connected devices can highlight use errors and compliance with therapies, and, therefore, can be used as a tool as part of the process towards improvement in the delivery of almost any therapy.”

Most critical aspects of connectivity

“The most critical aspect to connected drug delivery is improving patient adherence to get desired outcomes from prescribed medications,” says Bill Welch, chief technology officer, Phillips-Medisize. “First and foremost, connected drug delivery is about creating an engaging experience so that patients have the best tools and technology available to help manage their disease.”

Traditionally, the connectivity interface was built into the delivery device, such as medication reminders, timers, and alerts, notes Welch; however, with smartphone apps, it is now possible to further enhance the patient experience and the ability to share information. “With patient permission, information can be shared to the patient’s healthcare providers and even family members,” Welch continues. “This dynamic enables the entire care team and loved ones to be equally invested in the patient’s health to improve adherence and outcomes within the greater scope of a connected care ecosystem.”

Lawton E. Laurence, director, Radical & Disruptive Innovation, West Pharmaceutical Services, iterates the importance of defining the limits of connectivity. “Connectivity is communication. Communication among
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devices, among stakeholders, and then between those two groups. Connectivity is not a panacea for the pain of poor patient adherence,” he says. “Without an intimate understanding of your target patient population, device connectivity may only shine a spotlight on the overall weaknesses of the product. Consider it as a tool that can help you more effectively collect information and execute on the appropriate mitigation strategies for your patients.”

However, once the appropriateness of a drug–device combination product for a specific patient population has been discerned, using connectivity to then target specific issues underlying non-adherence can be exceptionally effective, Laurence adds. “In the distilled words of Lord Kelvin, ‘What gets measured, gets managed’ and there is no doubt that transforming the drug delivery space from one of ephemeral delayed reaction to a data driven ecosystem of aligned stakeholders is the core promise of connectivity,” he states.

“In order to consider the impact of connectivity on adherence, we should first explore what factors affect adherence,” remarks Meliniotis. By way of an example, Meliniotis referenced a research paper on inhaler adherence, which noted that although adherence can simply be defined as to how a patient follows a prescription, there are many variables, such as dose frequency, taste, and route of administration, that can actually influence the use of a medication (6).

“With regards to therapies where connected drug delivery can provide otherwise non-existent feedback, connected devices can provide both feedback and metrics to encourage patients to comply, changing their mind-set,” Meliniotis continues. “Gamification can be used, which uses an app or other feedback interfaces to encourage compliance, and there are suggestions that to ensure long-term compliance, constantly changing aspects, (i.e., new targets or ongoing metrics) can keep patients interested, and have a longer-term effect than more basic systems.”

“To be sure, the ability of connectivity to improve patient adherence in the short term has discrete merit; however, the real payoff is how we can leverage the information to feed the next generation of drug-device combination products,” adds Laurence. “The first movers will be privy to a treasure trove of usability information and their ability to operationalize that intelligence will position them to be the leaders in the next generation.”

Focus areas
“Connected drug delivery should be focused on areas where the impact can be the largest,” explains Meliniotis. “One example is by providing immediate feedback to a therapy that would otherwise be unavailable, for instance, an asthma maintenance therapy, where adherence may be poor due to no immediate decline in health, rather than insulin injections for diabetes, where adherence is generally high due to immediate severe outcomes.”

Adoption of connected solutions is already being seen in the fields of certain rare and orphan diseases, where there is a high cost per patient per year, Welch confirms. “Outcomes are important as payers move pharma toward performance-based contracts. Having confidence in patient adherence and the ability to get the best outcomes has, therefore, never been more important,” he adds. “Connected drug delivery can help facilitate outcome optimization by providing real data to healthcare providers to better informed treatment decisions.”

Other areas that can particularly benefit from connected drug delivery solutions include chronic diseases that need to be managed hourly or daily and for patients that require more acute care or rescue devices for emergency use, Welch notes. “Better ways to manage chronic, orphan, and emergency conditions with connected drug delivery are being looked at currently,” he says. “It is not a ‘one-size-fits-all’ solution, rather the connected health ecosystem must be built for the appropriate mitigation strategies for your patient population and even according to patient technique and identification.”

“Some therapies can be impacted significantly by user technique and identifying this can have a dramatic effect in the efficacy of treatment, particularly if it prevents a patient being prescribed a medication at a higher level in order to compensate,” agrees Meliniotis.

Taking into account how bio/pharma companies investing in connectivity could drive superior solutions in the future, Laurence stresses that one of the most underreported opportunities in connected devices relates to clinical trials. “If you want to study the adherence of your patient population and even access unassailable retrospective dose data, a mere notification in their patient-facing app presents a revolution in cost and time to collect that data,” he states. “It may be feasible to look at how changes in formulation, device characteristics, or nurse interventions impacted a patient’s adherence. Gone will be the days of supposition reaction; connectivity will usher in data-driven therapy evolution.”

Potential limitations
There are a couple of prominent limitations of connected drug delivery solutions, namely cost and environmental waste, explains Welch. “When electronics and sensors are added to make a traditional mechanical drug delivery device digitally connected, this drives up the cost. So, it is important to find a balance between the value of data and patient adherence versus the added cost of the electronics and sensors,” he notes. “Likewise, while the traditional single-use or disposable devices may have cost production advantages, companies and consumers should also consider the impact of a disposable device on the environment.”
It is the industry’s dependence on disposable devices that Laurence states as being the most insidious of limitations. “It is imperative that a sustainable solution is found that can improve a patient’s experience while reducing the burden on the ecology,” he says. “Another pressing barrier to connected solutions is patient trust in what will be done with the data collected by the device. Success will be unattainable if industry acts in a clandestine fashion on this matter. Every moment the security of drug delivery devices is called into question will be the nucleus of setbacks in our mutual goal to improve the standards of the patient.”

With many connected drug delivery solutions currently taking the form of an ‘add-on’ feature to an existing product, functionality is limited somewhat as the base device has not been originally designed with connectivity in mind, asserts Meliniotis. “As time progresses, delivery devices are likely to be increasingly designed with connectivity in mind, which could open up possibilities for integrated connectivity of high functionality add-on devices,” he states.

**Tips, tricks, and trends**

Some key considerations when developing a connected drug delivery device include optimization of the patient experience, significant market research to achieve a detailed target product profile, and taking a holistic approach with platforms and technology providers. Data privacy and security must also be considered thoroughly, particularly in light of the current focus in this area, continues Welch. “Pharmaceutical drug delivery devices are highly regulated and you have to be cognizant of the diligence and development rigor required on the device, the app, and the data access portals to meet the underlying regulatory criteria,” he says.

Looking at potential trends for the future, Laurence noted the movement toward advanced therapies, which is driving elevated prices. “It is increasingly important to be able to prove quantitatively the value being wrought in these therapies,” he says. “Pay for results and accountable care organization models are becoming more commonplace and connected drug delivery devices will be another wave of the same swell.”

For Meliniotis, the full potential of connected devices will only start to be unlocked once ‘true adherence’ is measurable. “Once devices are capable of measuring signals from the patient, monitoring ‘true adherence’, and automatically administering or prompting administration of medication, it will be possible to attain a closed feedback loop, which could ultimately optimize efficacy for patients individually,” he states. “Once the benefit of connected devices has been clearly demonstrated, pharmaceutical companies will invest more heavily in this field.”

“Another avenue for future trends is to consider the impact of prescription digital therapeutics as a combination with traditional injectables,” adds Laurence. “Like many things, it’s possible the combination of the two is significantly more powerful than either could be alone.”

Sustainability is high on the agenda for the future in Welch’s opinion. “There’s a real push from the industry, especially in the European regulatory environment, to manufacture products that are more sustainable and environmentally friendly from both a raw material utilization standpoint, but also in regard to the supply chain, logistics, and transportation considerations,” he adds. “Developing connected devices that achieve a balance between disposable and reusable will, therefore, be highly desirable. Sustainability, connectivity and cost must all come together to address the trends shaping the future of patient care with more efficient drug delivery that leads to better outcomes.”

“It would be difficult to describe a future state where every therapy wouldn’t benefit from connectivity,” Laurence continues. “The back-end infrastructure to convey the value to the stakeholders isn’t necessarily available today, but I’m quite certain it will be.”

Even though it is now possible, as it never has been before, to easily track aspects of drug delivery, it must be remembered that the effectiveness of any treatment is a combination of numerous factors, emphasizes Meliniotis. “As the availability of connected devices increases, so the effect of this data-driven therapy adjustment is likely to become increasingly apparent, which in turn will increase the desire to connect more therapies,” he says.

“At the end of the day, it’s all about accountability,” confirms Welch. “There are several dimensions of connected health that contribute to the overall picture. Creating a better user experience with a connected drug delivery device that drives higher patient engagement and ultimately improves health outcomes is the end game. To get there, everyone involved must assume a level of accountability.”

For pharmaceutical companies, accountability lies in providing drugs and connected delivery systems that can demonstrate improved outcomes supported by data, while the device manufacturers are accountable to their pharmaceutical partners to design and develop innovative products that optimize patient engagement, lower the cost of connectivity, and reduce waste, Welch emphasizes. “As the world becomes more connected, we all must do our part to keep the population—and the environment—healthy,” he concludes.

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The correct mix of excipients is crucial to the success of fast dissolving/orally disintegrating dosage forms.

Today, FDA expects drug formulators to not only consider patients outcomes when developing new products, but to also focus on the overall patient experience. Four main factors address the patient experience, according to Sarath Chandar, chief science officer with SPI Pharma: convenience, compliance, safety, and efficacy. Orally disintegrating tablets (ODTs) and other fast-dissolving oral dosage forms address the first two factors—and to some extent efficacy as well—from the standpoint of sublingual delivery, which can lead to increased bioavailability for poorly soluble APIs.

Convenience is increased with ODTs and fast-dissolving products across all patient populations. “Pediatric patients benefit from this group of products because they dissolve faster than what they are able to spit-out and can also be mixed with foods for easy administration. These products can also be taken without water, so they are also amenable for adults on the go,” says Krizia Karry, global technical marketing manager at BASF Pharma Solutions.

The fact that ODTs do not need to be washed down with water provide additional benefits as well. ODTs are, for instance, attractive to those who do not want to swallow liquids or hard tablets because they are feeling nauseous, adds Ralph Gosden, head of product development at Catalent Swindon. They are also useful when there is a need for rapid drug release, such as to relieve a headache, according to Torkel Gren, science and technology officer for Recipharm. “Orally disintegrating products are an ideal platform for delivery of active ingredients for the treatment of pain, allergies, diarrhea, Parkinson’s disease, travel-related illness, and other indications where rapid dosing and absorption is required,” he observes.

In addition, ODTs can help patients who have an aversion to swallowing a tablet or capsule, and those who find it extremely difficult to take standard tablets because they may have dysphagia or other problems with swallowing (e.g., the elderly and infirm), Gosden notes. “Patients suffering from mental impairments can benefit as well,” he adds, “as they will sometimes deliberately avoid taking medications or pretend to have swallowed a standard tablet or capsule by hiding it in their mouth to spit out later—a practice referred to as ‘cheeking’. This tactic is nearly impossible with an ODT as it disintegrates quickly and completely.”

Other benefits of orally disintegrating products in some cases are higher bioavailability and the fact that faster drug uptake can be achieved, according to Gren. “Instantaneous disintegration allows the drug to be dissolved and absorbed more rapidly, and for drugs that can be absorbed via the mucous membranes within the oral cavity, it can help to avoid the harsh environment within the gastrointestinal tract and bypass first-pass metabolism by the liver.”

Films, granules, and tablets

Orally dissolving products include tablets, granules, and films. “For tablets, the most common manufacturing technology is direct compression into tablets or minitablets,” Karry asserts. The use of 3D printing is also being explored for the production of ODTs, Gosden notes. “Granules are mostly produced via fluid bed granulation/drying and twin-screw granulation to ensure adequate size control. On the other hand, films are cast and dried on moving Teflon membranes from solutions or suspensions of APIs and soluble polymers,” Karry comments. More advanced technologies are often protected by patents, which may restrict competition, according to Gren. “In addition,” he stresses, “a more com-
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plex technology should not be used if it does not result in significantly better product properties.”

Thin film strips are a delivery technology that can be used for both systemic and local delivery by oral, buccal, and sublingual routes, according to Gosden. “Although they dissolve rapidly in the mouth and are considered self-administrable, the application of thin-film strips is somewhat limited as the maximum dose that can be formulated for delivery via the digestive tract is only in the 20–50 mg range,” he says.

In addition, Chandar adds that FDA has not approved many thin-film products for pharmaceutical applications because the strips can stick together, resulting in the patient taking multiple doses at once. This challenge has been addressed by individually packaging the oral strips, according to Karry.

The distinguishing properties between orally dissolving products are the form factor and drug delivery methods (e.g., sublingual, buccal, oral, etc.). “The form is selected taking into consideration the target population and the API solubility. For example, a drug dissolved in a polymeric matrix in the form of a fast-dissolving film may avoid first-pass effects through buccal drug delivery and thus show higher bioavailability due to the design of the drug product,” Karry says.

Several distinguishing features
To be successful, orally disintegrating formulations must have certain features. The most important property is rapid—within 30 seconds or less—disintegration or dissolution in the oral cavity with or without water, according to Chandar. Because they are placed in the mouth, they also ideally should have a pleasant mouth feel that is creamy rather than chalky. An attractive taste is also ideal, which requires taste masking if the API is bitter, which many are.

Excipients: The most important component
Excipients are the most important part of orally disintegrating/fast-dissolving products, according to Karry, because they ensure good sensory properties and adequate technical performance. “When developing conventional tablets, the drug developer will focus on a limited number of characteristics that are easy to measure quantitatively, such as hardness, friability, disintegration, and in-vitro dissolution. When working with ODTs, several parameters that are difficult to measure are affected by the excipient,” Gren explains.

A pleasant mouth feel, rapid disintegration, and acceptable taste are crucial characteristics.

“Examples include creating a clean mouth feeling, or creaminess and overall good palatability, as opposed to grittiness and lingering bad flavors, all the while leading to tablets with high tensile strength, low friability, and fast disintegration,” Karry says. She also points out that the interplay between tensile strength and disintegration is particularly important, because the stronger the tablet, the lower its porosity and the slower it disintegrates. “In this case, having both an efficient binder and a super-disintegrant is necessary for good performance of the drug product,” she comments.

Compressed tablets require super-disintegrants, which either swell orwick up saliva, disrupting the tablet’s structure and encouraging dispersion, according to Gosden. Other important excipients include binders and fillers, according to Karry. Numerous other excipients can also be added to impart specific properties, such as lubricants, sweeteners, colors, and flavorings. “However,” Gosden notes, “some of the additional ingredients that may be required to manufacture the tablet can impede its disintegration. For example, if high levels of lubricant are necessary, the particle size must be carefully considered. If the particle size is too large, then the tablet may give a gritty and unpleasant mouthfeel as it disperses.”

Certain excipients also enhance the bioavailability of poorly soluble APIs (e.g., Biopharmaceuticals Classification System [BCS] II and IV) by helping to increase the dissolution rate, according to Chandar.

Selecting the right excipients
The type and amount of excipient needs to be carefully selected in order to get the right balance between a number of technical characteristics, including stability, flavor, and mouthfeel, Gren comments. It is particularly important to choose the right filler(s), he says, because the filler is often present in large quantities and has a significant impact on the taste and mouthfeel of the product. “A judicious use of quality-by-design and multivariate methods are helpful here,” notes Gren.

Some excipients found in orally dissolving products such as sweeteners and flavoring agents are not normally used in conventional tablets, according to Gren. “Here it is extremely important to work in close collaboration with the marketing professionals when selecting the type and amount of all excipients, but especially the flavoring agents. The taste of the product should be developed in order to suit the intended patient population,” he says. “In my experience, sugar alcohols, mannitol in particular, are extremely useful in orally disintegrating products; they provide sweetness and pleasant mouthfeel and also have relatively favorable technical properties,” Gren observes.

The most important excipients are those that ensure adequate technical and sensorial performance, notes Karry. She lists binders to give strength to the formulation, super-disintegrants to ensure fast hydration and disintegration, taste-masking polymers to decrease the interaction between the bitter or acidic drugs and tongue receptors, and flavors, which are used as needed based on the target population and to stimulate saliva secretion. Strawberry and apple flavors stimulate more saliva than cinnamon, for example.
“The absolute most important excipient for these products, in my opinion, are disintegrants,” Karry says. “As a patient, I can accept having a bad tasting medicine—there are many out there already—but what I cannot accept is having a bad taste in my mouth for minutes or hours. Disintegrants help to ensure this does not happen. They enable complete drug product disintegration in the mouth so that the small particles can be swallowed, and if designed right, they clean our mouth as well,” she explains.

Karry notes that studies have shown that both particle size and shape play an important role in mouthfeel. Hard irregular particles are perceived as larger than soft and smooth particles (1), while particles of 100 µm in size are perceived as creamy or fatty and thus activate salivary secretions and swallowing (2). “These studies demonstrate that a systematic science-based approach is needed when formulating orally disintegrating products,” Karry concludes.

For lyophilized ODTs, Gosden says the most critical excipients are those that form the porous structure, specifically gelatin and mannitol. “While the freeze-drying process is under way, it is important to ensure that all of the mannitol remains crystalline, or there will be a risk that the finished dosage form will collapse during storage,” he explains.

Chandar notes that for poorly soluble APIs, surfactants and plasticizers are used for bioavailability enhancement. He stresses, though, that no excipient should be used unless there is a demonstrated need and each ingredient in an ODT formulation should be justified.

It is also worth noting, according to Gosden, that some excipient suppliers have developed proprietary blends of excipients in ready-to-use form (i.e., co-processed excipients) for the creation of compressed ODTs.

**Synergies with co-processing**

Co-processed excipients based on microcrystalline cellulose (Prosolv ODT from JRS Pharma) and mannitol (Ludiflash from BASF and Pharmaburst from SPI Pharma) have been increasingly used in orally disintegrating/fast-dissolving products owing to their ease of use and overall particle characteristics, according to Karry. “In particular,” she observes, “those containing mannitol have the advantage that this alcohol sugar has a negative heat of solution and upon dissolving in the mouth imparts a cooling effect with a sweet taste. Mannitol is also amenable for ketogenic diets (important for epileptic patients) and diabetics (due to the low carbohydrate count).”

Co-processing, unlike simple blending or mixing, of different excipients, enables the enhancement of functional performance, according to Chandar.

**Excipients should be selected based on technical, stability, and patient adherence requirements.**

“Whether via spray drying, granulation, congealing, or other methods, co-processing—when done effectively—creates synergies between the excipients involved, leading to unique properties and functionality not achievable any other way,” he states.

As an example, Chandar points to SPI Pharma’s latest addition to the Pharmaburst line (500), in which the excipients are subjected to a three-step process that includes spray drying and granulation. “The result is a microplate structure of the combined excipients that exhibits a 30–40% improvement in compactability compared to simple, physical mixing. This higher compactability opens up a broader design space for formulating robust ODTs by providing a much higher API carrying capacity of up to 500–600 mg,” he remarks.

**Other important advances**

Catalent has developed Zydus Ultra, a next-generation ODT technology that provides better taste-masking properties in a lyophilized ODT combined with an increased drug loading capacity, according to Gosden. A coating is applied to the outside of micronized API particles (as small as 100 µm in diameter) using a dry-coating process.

“Gelatin forms the overall polymeric structure of the tablet, while mannitol increases robustness and makes the tablet look aesthetically elegant. Both ingredients dissolve readily in saliva, giving a quick-acting, melt-in-the-mouth experience for the patient,” Gosden says. In addition, he observes that unlike compressed ODTs, they are not reliant on the use of super-disintegrants to provide rapid dispersion. Instead, the rapid disintegration results from the way in which lyophilized ODTs are manufactured as well as the formulation of excipients.

BASF, meanwhile, has developed Kollidon CL-SF, a superfine disintegrant with unique properties for ODTs, according to Karry. “This super-fine version of crospovidone was specifically designed to provide formulators a disintegrant that generates upon hydration smooth particles that are less than 100 µm for a non-gritty, melt-in-your-mouth feeling,” she explains.

Separately, Karry notes that many companies in South America and Europe are moving to twin-screw granulation methods for manufacturing fast-disintegrating granules. “Twin screw allows for better control of granule size and is easily converted and integrated into continuous manufacturing processes,” she says.

Regardless of the technology, the advantageous properties of new and more advanced excipients should be balanced against the higher costs that are often associated with them, asserts Gren. “For example,” he comments, “a more expensive excipient may allow you to avoid complex process steps and hence reduce manufacturing costs. As a result, the overall costs must be considered.”

Contin. on page 60
Possibly the most publicized and well-documented form of drug misuse and abuse has been that of opioids—prescription pain-relief medicines. The opioid crisis, which has impacted the global health community for several years, has paved the way for increased demand in abuse-deterrent formulations from pharmaceutical developers.

Abuse-deterrent formulations essentially have the potential to provide an effective way of reducing the capabilities of an end-user to abuse or misuse a medical therapy, while maintaining the drug’s clinical benefit. To explore the topic of abuse-deterrent formulations in more detail, Pharmaceutical Technology spoke with Angela Moore, scientist, Analytical Development, Alcami.

**In need of risk mitigation approaches**

**PharmTech:** Could you discuss some of the reasoning behind abuse-deterrent formulations and why there may be an increase in interest in this area?

**Moore (Alcami):** Doctors continue to prescribe opioid medications for pain management, generating an inevitable association with abuse and addiction. Government officials and pharmaceutical professionals alike are in need of risk mitigation approaches.

In the United States alone, there have been estimates, released by the US Department of Health and Human Services (HHS), revealing that in 2018 over 47,000 citizens died from an opioid overdose and that two million people in the country were suffering from an opioid use disorder (1). The economic costs associated with the opioid epidemic have been estimated at $504 billion, according to analysis by Johns Hopkins University Bloomberg School of Public Health (2). And, the issue of opioid addiction is not isolated to the US, with countries worldwide experiencing significant healthcare costs associated with prescription opioid abuse, such as those experienced in the five largest European countries as reported by Shei et al. (3).

Pharmaceutical companies have responded to this need through more stringent abuse-deterrent formulations and studies. Although abuse-deterrent does not equate to ‘abuse-proof,’ medications that contain abuse-deterrent properties make it more difficult for abusers to obtain the euphoria associated with common manipulation techniques.

**Current approaches**

**PharmTech:** Currently, what abuse-deterrent formulation approaches are available and what are the benefits and/or limitations to these approaches?

**Moore (Alcami):** The current products on the market that contain abuse-deterrent labeling approved by the Food and Drug Administration fall into two categories of abuse-deterrence: physiochemical and opioid/antagonist. Physiochemical abuse-deterrent properties include products that are formulated to resist crushing, chewing, and physical manipulation. They contain excipients that will ‘gel’ upon contact with solvents to make them difficult to inject intravenously. Opioid/antagonist products contain the active opioid intended for therapeutic use and also a sequestered antagonist so that if the product is manipulated intentionally it will release a chemical that will prevent the user from feeling the euphoric effects of the opioid.

There are benefits and challenges to both physiochemical and opioid/antagonist abuse-deterrent formulations. Benefits of physiochemical formulations include having physical barriers that make it more difficult to resist tampering and manipulation. Abusers...
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avoid these formulations as they cannot easily crush and/or inject the drug. One of the biggest challenges of these types of formulations, however, is that there are still drug abusers who find ways to abuse these products. The excipients that are present in the formulations to prevent abuse can cause many health issues if injected. For example, OpanaER (Endo Pharmaceuticals) was an extended-release oxymorphone hydrochloride oral drug product. The drug was approved by FDA in 2006 but was being abused mainly by injection. The drug was reformulated in 2010 with physiochemical properties intended to be resistant to intranasal and intravenous routes. However, in June 2017, FDA requested OpanaER to be removed from the market as abusers had moved from insufflation abuse to injection abuse (4). The reformulated drug product was being shared between multiple users for injection. OpanaER was directly linked to outbreaks of Hepatitis C (New York, 2011), thrombotic thrombocytopenic Purpura-like (TTP) illness (Tennessee, 2012), and HIV (Indiana, 2015) (5,6).

A benefit to opioid/antagonist abuse-deterrent formulations is that the drug product contains a sequestered antagonist within the formulation. If the drug product is administered to patients as intended, it will work therapeutically. However, if a drug abuser tried to crush or manipulate the drug, the sequestered antagonist would be released and block the euphoric effects of the opioid. However, these abuse-deterrent products are not ‘abuse proof.’ Drug abusers have found ways to chemically extract the opioid from the antagonist with common household solvents to still abuse these formulations.

Another challenge that is related to all of the eight approved, abuse-deterrent opioid products that are on the market is cost. The products are all name-brand and expensive to patients. There are currently no FDA-approved generic equivalents to abuse-deterrent formulations, and insurance companies are reluctant to pay the extra expense for an abuse-deterrent opioid when the cost is vastly different from generic non-abuse-deterrent equivalents.

Close regulatory scrutiny

PharmTech: Are there specific regulatory challenges that should be considered when approaching abuse-deterrent formulations?

Moore (Alcami): FDA is closely scrutinizing all new abuse-deterrent products and current opioid products that are on the market now. There are comprehensive, in-depth testing requirements prior to approval of these products. For example, in-vitro testing of products intended to prevent abuse can take six months to a year to complete thousands of extraction, manipulation, and syringe studies.

“it is not uncommon for FDA to request additional testing.” —Angela Moore, Alcami

After this testing is complete, the products are then verified in a clinical setting in humans, where clinical subjects purposely take a product as intended and then in an abused form and rate their ‘drug liking,’ which is if they enjoy the product recreationally and if they would take the drug again.

Post-approval, FDA also requires all pharmaceutical companies that manufacture prescription opioids commercially to participate in the REMS program (Risk Evaluation and Mitigation Strategy) where they monitor the abuse of commercially marketed opioid pharmaceuticals.

As each formulation and mode of abuse can be different, there is only FDA published guidance, Abuse Deterrent Labeling—Evaluation and Labeling Guidance for Industry, published in April 2015 that pharmaceutical companies can use as a guide for completing the required tests. Companies must work closely with FDA to ensure the testing performed is adequate and that study designs are acceptable. It is not uncommon for FDA to request additional testing at each stage of studies, which takes considerable time and expense to execute.

Evaluating effectiveness

PharmTech: How can the effectiveness of an abuse-deterrent formulation be evaluated?

Moore (Alcami): Current FDA guidelines for determining abuse-deterrence of a drug product involve four main studies termed Category 1, 2, 3, and 4.

Category 1 testing involves laboratory manipulation and extraction studies. In these studies, the product is evaluated and compared to currently marketed formulation(s) for the ability to defeat or compromise the abuse-deterrent properties. This testing is performed in-vitro and provides physical characteristics of the product and its ability to resist crushing, grinding, melting, and so on, to inhibit nasal abuse. Extraction studies provide information on the product’s ability to isolate the antagonist, or resist abuse by injection, or, in larger volumes, resist abuse by ingestion.

Category 2 testing involves pharmokinetic studies in healthy humans. The product’s in-vivo properties are evaluated by comparing an intact formulation against the manipulated formulation through one or more routes of administration. Comparator products are also evaluated for comparison.

Category 3 testing evaluates the clinical abuse potential of the product. These are large, complicated in-vivo studies that are generally conducted with recreational drug users as test subjects. These test subjects are screened prior to the study to ensure that they are able to distinguish between active drug and placebo in a drug abuse setting. In these studies, the test subjects are provided with the drug product being developed and suitable comparators. The drugs are administered through the route of abuse that is being studied (i.e., oral or intranasal) and the patients provide not only pharmokinetic data, but also...
subjective data on the drug liking (how high they are) and if they would take the drug again.

Category 4 assessment is a post-approval study that determines if the product has resulted in meaningful reductions in abuse, misuse, or adverse clinical outcomes (addiction, overdose, and death). These evaluations are conducted by the product manufacturer. Currently, there are no products on the market that contain the Category 4 label for abuse-deterrence.

Many considerations

PharmTech: What trends, potential new approaches, and considerations do you foresee as being important in the field of abuse-deterrent formulations in the near future and why?

Moore (Alcami): One of the biggest trends in abuse-deterrent formulations is the development of abuse-deterrent generic products. FDA has published guidance for industry, *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*, for companies that are developing generic products comparable to the approved abuse-deterrent products on the market (7). The intention of the guidance is to reduce the amount of testing required for the generic product by showing equivalence or superiority to the name-brand product in laboratory-based, abuse-deterrent tests so that human trials (Categories 2 and 3) are not required. Additionally, any new opioid drug that is being developed must demonstrate resistance to abuse in order to grant FDA approval.

There are many considerations for manufacturers developing abuse-deterrent opioid formulations. Most importantly, the product must be considered safe and effective, and it must adhere to all regulatory manufacturing and testing guidelines. From a chemistry and biologic perspective, the product must resist dose dumping and abuse, but still release the active ingredient when ingested as intended. From the commercialization perspective, key considerations are developing a product that has a competitive advantage over what is on the market today. The company must differentiate their product so that they can answer the question: ‘What product characteristics will make a doctor want to prescribe the new product over what is on the market?’ Furthermore, insurance companies, governments, and patients must be convinced that the new product is worth more compared to cheaper, non-abuse-deterrent products on the market.

References


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Why Do Disinfectant Residues Matter?

Madison Hoal and Donald Singer

Consider how to assess risks and understand possible sources of disinfectant residues.

In aseptic manufacturing, the application of cleaning and disinfection agents reduces contamination to an acceptable level for the grade of cleanroom and prevents cross-contamination from surfaces that are part of or adjacent to good manufacturing practice (GMP) manufacturing operations. There is systemic complacency within the industry regarding the cleaning and disinfection products used and the associated program. A common response within industry when asked about the rationale for a given cleaning regime is: “We have always done it that way.” When a review of the associated environmental monitoring trends demonstrates a degree of control, everyone is satisfied.

Historically, cleaning has been the “residual contaminant” removal step and disinfection has followed, often at times leaving the disinfectant on the surfaces indefinitely. Legacy cleanroom environments were often following the old adage that “visible disinfectant residues on the surface are a preventative measure.” But this rationale may be changing. The authors have seen a prolonged and increased concern from regulators over residues left from disinfectants post-application.

Current industry thinking, along with recent compliance mandates (1), is that any residual chemical is a potential chemical or particulate contaminant to a process and possibly to product. This renewed focus has led a change from legacy thinking to a consideration of how to assess and address disinfectant residues, including an evaluation of what properties other than efficacy, such as residue profile, should be considered for cleaning and disinfectant products.

Considering risk

Product quality risk. The presence of a disinfectant residue represents a risk to product quality as either a physical or chemical contamination risk, which is why products such as alcohols are commonly used in close proximity to open product, as they leave little or no residues. For aseptically produced and low-bioburden products, contamination control is intertwined within the quality system, facility design, and process validation. The US Pharmacopeial Convention (USP) says (2):

“The removal of residual disinfectants should be monitored for effectiveness as a precaution against the possibility of product contamination.”

Cleanrooms are typically designed to facilitate contamination control for pharmaceutical products at the point in the manufacturing process where internal controls are most important. The highest risk products, sterile injectables, require product contact surfaces to be contamination-free and are commonly subjected to validated sterilization processes. Adjacent surfaces on production machinery and containment equipment (e.g., isolators or restricted access barriers) can be decontaminated, with the assurance that residual agents are removed, to prevent possible cross-contamination during the filling process where product is minimally exposed.

Biopharmaceutical cleanrooms can range in use from bulk manufacturing, containing large tanks/vessels and complex purification equipment, to fill/finish operations for sterile injectables. The concern with residual disinfectant cross-contamination into product processing is a moderate risk in bulk manufacturing areas, unless product processes are directly adjacent to a decontaminated surface, such as a fermentation tank with any size hatch that can open. Filling operations are similar in high risk to the sterile injectable.

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tainment features to protect the live cells and inherently short manufacturing times, yet there are still many surfaces that need to be part of the contamination control strategy. These surfaces are disinfected routinely with expectations that no residue exists that can be carried by operators (on their gloves or gowns) or mobile equipment from one activity to another in the manufacturing suite(s). Appropriate choice of disinfectants is also crucial when using single-use bags containing live cells throughout the life cycle of a cell therapy.

Despite the expectation that no disinfectant residue exists in these critical and adjacent manufacturing areas of any type of pharmaceutical operation, broad-spectrum disinfectants and sporicidal agents used in these same areas often leave residue, which may or may not be visibly apparent.

The new draft of Annex 1 contains a specific regulatory guidance statement about disinfectants, which highlights that cleaning programs should be effective at removing disinfectant residues. This expectation is in line with the developing expectations of industry and with historical regulatory observations. Annex 1, section 4.36 says (1):

“The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, prior cleaning to remove surface contamination should be performed ... Cleaning programs should effectively remove disinfectant residues.”

**Regulatory risk.** Regulatory compliance is always a business expectation because of its impact on final products and the patients who are the primary customers. Regulatory inspections follow the legal requirements stated in practical terms as current good manufacturing practices (CGMPs). Inspectors have authority to interpret CGMPs when they evaluate a manufacturing operation.

Evaluation of cleaning and disinfection practices are part of the CGMP inspection. Most evaluations of the cleaning and disinfection program are based on visual observation. Inspectors will not only indicate and question visual observation of residues from product, but they also will note disinfectant-type residues. Since cleaning validation usually relates to product contact surfaces, most non-product contact surfaces do not have a quantitative analysis of residues. Thus, the visual observation of residue by an inspector is often generalized and unqualified as to its identification as a residue from manufacturing products (actives or excipients), cleaning, or disinfection. Notation of color and location is often the extent of an observation, which leaves the identification of the residue and the subsequent corrective action with the manufacturer. In most situations, residue of any kind becomes an observation/finding from the inspection with a requirement to identify and mitigate/prevent future occurrence.

**Health and safety risks.** Another aspect to consider is the health and safety risk disinfectants may have on cleanroom operators and cleaning technicians. All disinfectants are by their very nature toxic to living organisms; however, these chemicals are an effective and safe tool when handled appropriately with adequate safety measures in place. Training on proper storage, mixing, handling, and application procedures is essential.

The interaction between some disinfectants can lead to undesirable risks to cleanroom operations. If the cleaning and disinfection program does not address disinfectant residues prior to applying different chemistries, there is a potential for chemical interactions between the chemistries in use (3). For example, a chlorine-based disinfectant applied after a phenolic-based disinfectant may result in the release of toxic chlorine gas. Additionally, these chemical reactions may also interfere with the disinfectant’s efficacy. The presence of disinfectant residues may also reduce the biocidal activity of disinfectants subsequently applied to the surface. This may result in frequent environmental excursions or increased recovery of microorganisms that the cleaning and disinfection regime should have been effective at managing throughout the facility.

Disinfectant residues can also interact with one another, causing sticky or slippery floors. Both outcomes pose a risk of slips, trips, and falls to cleanroom operators. In addition, the presence of sticky floors may also lead to the accumulation of debris on the surfaces, posing a gross contamination risk. It is imperative that pharmaceutical manufacturers review their cleaning and disinfection program to ensure that a residue removal step is incorporated when changing or rotating between different disinfectants, such as prior to sporicides.

**Facility risk.** Cleanroom operators are sure to have seen evidence of disinfectant residues, such as an oily sheen on stainless steel or the chalky white powder on the floor covering. Other effects from the use of disinfectants on cleanroom surfaces can be rouging on stainless steel or the reduction of the epoxy floor sheen.

In cleanrooms, disinfectant residues are often monitored, or measured, visually. These residues, if not managed preventatively, can cause degradation to the facility over time, which can lead to costly reconstruction or require deep cleaning measures.

A significant source of facility degradation tends to be rotational sporicides. Due to effective use levels of sporicidal formulations, these chemicals tend to be corrosive in nature and can quickly age a facility if not appropriately managed. It is crucial that the residues of these types of chemicals are removed from the surface after the appropriate contact time to
avoid degradation over time. However, it should be noted that residue should not only be removed from cleanroom surfaces where the residue is visibly apparent, such as on stainless steel and glass, but also on surfaces where the residue may not be visibly apparent, such as non-reflective surfaces.

**Consumption of time and resources.** The disinfection residue removal process is likely to require additional time and resources in the form of increased cost of labor and supplies to remove residues, which in turn leads to reduced production time and productivity.

### Controlled application is important on surfaces. Multiple coatings and overlapping the same surface serve as a potential cross-contamination issue and contribute to residue build-up.

**Factors leading to residue**

Disinfectant residues need to be removed from the cleanroom environment, but most disinfectants have some degree of residues. It begs the question: How can cleanroom operations meet the regulatory requirements without impacting their production schedule and targets?

Several aspects of the cleaning and disinfection program can be reviewed to reduce the impact and/or risk posed by disinfectant residues, such as introducing a residue removal regime, reviewing application techniques, and choosing low-residue formulations.

**Insufficient or non-existent residue removal.** All disinfectants, with the exception of some isopropanol and hydrogen peroxide formulations, leave some amount of residue on the surface, which will require routine residue removal.

Cleanroom disinfectants are typically aqueous-based formulations and are therefore readily dissolvable in water. Thus, the best solvent to remove disinfectant residues is water. Normally, this is water for injection or purified grade water, depending on the location and risk to the cleanroom. However, water poses another risk to the cleanroom: origin or potential for microbiological growth. To address this concern, 70% alcohols are commonly used in critical environments. While 70% alcohols are disinfectants, they are also used to reduce the build-up of other disinfectant residues.

The effectiveness of the residue removal step should be assessed for each disinfectant used in the site’s cleaning and disinfection program. The frequency of the residue removal will depend on the means of application and the disinfectant formulation.

**Over-application.** When applying disinfectant to cleanroom surfaces, the end-user should be cautious of oversaturating a surface. Over-application can be the result of many common challenges within the cleanroom. One challenge is achieving the validated contact time. A heavy application of disinfectant may seem like a way to achieve the validated contact time. However, by oversaturating a surface, more disinfectant is being applied, resulting in more disinfectant residues building-up over time.

Another common challenge is improper use of the cleaning and disinfectant tools. The user should seek cleaning and disinfecting tools that apply the disinfectant in a controlled manner, such as an effective wringer and a defined saturation level for wipes. If controls are not in place, variability in application can result among operators, which in turn can impact effectiveness of the cleaning and disinfection program. Over application can also impact the frequency of the residue removal program.

Manufacturing sites should also ensure that their cleaning and disinfection personnel are adequately trained to apply disinfectants in a cleanroom setting. This includes training on the saturation level of mops and wipes, as well as how controlled application is important on surfaces. Multiple coatings and overlapping the same surface do not only serve as a potential cross-contamination issue, but also contribute to disinfectant residue build-up.

*Contin. on page 60*
Subcutaneous (SC) injection is a method of administering medication as a bolus under the skin that is often used as an alternative delivery method for oral administration and now also for high-dose administration through intravenous (IV) infusion. SC injection provides flexibility in dosage form and options of self-administration outside of a health care setting. It may also help reduce drug cost and increase patient compliance. Biopharmaceuticals intended for delivery as SC injections are commonly formulated at an acidic pH with a variety of stabilizing agents and buffers, including histidine, phosphate, and citrate. In addition, SC injections are limited by a maximum injection volume of 2 mL or less per dose, making SC injection of monoclonal antibodies (mAbs) challenging. MAbs require high dose; therefore, for SC injection it must be formulated at high concentration so the total injection volume remains within 2mL. An increase in protein concentration in the formulation increases the solution viscosity, which may cause increased injection-site pain in an SC dosage. The authors will discuss how formulations containing citrate compare to other buffers in reducing SC injection-site pain and discuss a formulation and excipients selection strategy that formulators can use to mitigate the risk of injection-site pain due to buffer, pH, and viscosity.

SC injection is currently the most common route of self-administering drugs, such as proteins and peptides (1). In these applications, patients are not administered drugs, but rather formulations that contain a drug. Subcutaneously injected drugs are often formulated in non-physiological conditions to improve or maintain product efficacy and stability throughout product shelf life (1, 3, 4). Biopharmaceuticals intended for SC injection are commonly formulated at acidic pH with a variety of stabilizing agents (4, 5). A typical SC formulation composition includes buffers (e.g., citrate, histidine, phosphate, acetate), tonicity adjusting agents (e.g., dextrose, glycerol, sodium chloride), antimicrobial preservatives (e.g., m-Cresol, phenol, benzyl alcohol) and stabilizers (e.g. salt, amines, buffers) and viscosity-reducing agents (e.g., arginine, histidine, polysorbate, human serum albumin, surfactants, zinc chloride) (6).

Injection-site pain challenges in the development of an SC formulation

While SC injection has numerous benefits, one potential drawback is that it may cause pain at the injection site. This may be caused by different factors, including buffer type, pH, temperature, viscosity, injection volume, tonicity, individual experience, speed of injection, needle size, anatomical region and formulation (2, 7, 8, 9, 10).
An inherent limitation of SC dosage form is the injection volume. The maximum volume that can be administered is typically less than 2 mL (2, 5), because the area available under the epidermis and dermis are limited in such a way that the injection of large volume creates high back pressure. Considering this limited maximum injection volume, SC administration of monoclonal antibodies (mAbs) at a high dose necessitates the development of stable, high-concentration formulations which may also have high viscosity. As viscosity increases, the time and pain at the site of the injection increase as well, making treatment challenging to administer while also negatively affecting patient compliance (11).

Pain at the injection site is also protein-specific (2). As reported by Schmitt et al. (12), a prospective, randomized, double-blind study demonstrated increased painfulness of subcutaneous injections for treatments of anemia. The study evaluated the effects of SC delivery of darbepoetin-α (commercially marketed as Aranesp, a trademark of Amgen) compared to epoetin-β (commercially marketed as NeoRecormon, a trademark of Roche) in children. The higher injection pain with darbepoetin-α, which cannot be explained by differences in injected volume, needle properties or patient anxieties, must therefore be related to the nature of the injected fluids per se (12). The meticulous standardization of and the higher injection pain with the preparation and injection procedure, as well as the double-blind design of the study, largely ruled out any interference by technical factors (e.g., needle, injected volume) or psychological factors (e.g., previous adverse experience with one of the drugs or biased pain expectation towards the new drug). Darbepoetin-α was usually diluted with twice as much saline as epoetin-β; this factor should, if anything, have reduced injection pain with darbepoetin-α. Hence, it is highly likely that the difference in perceived pain is related to the specific composition of the two medications (12).

In another example, a single-center, crossover study was designed to compare visual analog scale (VAS) scores associated with three 3.5-mL SC injection durations to that associated with a 1.2-mL SC bolus injection and to investigate tolerability, swelling, and leakage from the injection site (13). Results are shown in Figure 1. The study demonstrated that, immediately after administration and one hour later, a SC injection of 3.5 mL of a viscous placebo buffer, with the characteristics of a typical protein formulation, administered over one minute was associated with more pain than a 1.2-mL bolus injection. Administered over 10 minutes, it was associated with less pain than the bolus injection. The differences were not considered clinically meaningful, suggesting that it may be possible to reduce the number of injections per biotherapeutics treatment through the injection of larger SC dose volumes using a prefilled syringe, auto-injector or another personal injection device (13).

**Use of citrate in SC formulations and its impact on injection-site pain**

Formulation plays an important role in controlling pain at the injection site. For example, a histidine buffer is known to be less prone to cause pain upon injection compared to a phosphate and citrate buffer (2, 9, 10, 11). Figure 2 shows the results of a double-blind study of 54 healthy individuals who were injected with recombinant human growth hormones in two different commercially available solutions (histidine and citrate). An experienced nurse performed the injections pairwise (right and left thigh). A majority of the participants (38/54) reported that the citrate buffer caused more pain than the histidine buffer (11).

It is hypothesized that the pH of the injection site might not drastically change upon injection unless the formulation contains strong ions as buffering agents (1). This is supported by a study where it was reported that the pain patients experienced upon injection was more serious for citrate than for histidine or saline (11). Since citrate is a strong ion, whereas histidine and saline are not, it is possible that the pH shift within the SC tissue upon the administration of the buffers is more significant with citrate than with saline and histidine, resulting in a more painful injection (1).

Results of a randomized, double-blind, crossover study indicated that the epoetin alfa formulation using a sodium phosphate buffer was associated with less injection-site discomfort and a shorter duration of pain than the formulation containing a citrate buffer (14). An epoetin alfa formulation using sodium phosphate as the buffer may provide an advantage in local tolerability and compliance (13). These findings support the notion that SC injection volume is a critical factor in determining injection pain: smaller volumes yield less pain than larger volumes.

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**Figure 1.** Visual-analog scale (VAS) pain scores by treatment, immediately and one hour after administration. Dots represent means, boxes represent the first quartile to the third quartile with lines showing medians, and whiskers indicate ranges.
ings are consistent with other reports in the literature (15, 16). Human insulin-like growth factor I (hIGF-I) formulated at isotonic conditions with sodium chloride (NaCl), ranging in pH from 6 to 7 with phosphate buffer concentrations of 5 to 50 mM, was investigated to determine subcutaneous injection pain and local tolerance (redness, paleness, and edema). The discomfort at the injection site was lowest with 10 mM phosphate, pH 7. Injection of the buffer at pH 6 (50 mM phosphate) caused significantly more pain than using 10 mM phosphate, whereas the pain at pH 6 using 10 mM phosphate did not differ significantly from that experienced in the injection of the solution at pH 7 using either 10 mM or 50 mM phosphate. The hIGF-I itself did not seem to cause pain. The authors conclude that for subcutaneous injections at non-physiological pH, the buffer strength should be kept as low as possible to avoid pain upon injection. The authors also hypothesize that when a non-physiological pH must be used for stability reasons, lower buffer strength enables more rapid normalization of the pH at the injection site (17).

A single-blinded study with 42 adult volunteers employed at a tertiary care center was performed to determine the impact of administration rate and buffering on the pain associated with subcutaneous infiltration of lidocaine (18). Each subject received four lidocaine injections:

- slow, buffered (SB)
- slow, unbuffered (SU)
- rapid, buffered (RB)
- rapid, unbuffered (RU).

Buffering was accomplished by mixing 1% lidocaine with 8.4% sodium bicarbonate in a 9:1 ratio. Slow administration was 30 seconds and rapid was five seconds. Needle size (27-gauge), injection depth (0.25 inch), lidocaine volume (1.0 mL), and temperature (room) were the same for each of the four injections. In all four conditions, the needle remained in the forearm for 30 seconds to ensure blinding. The main outcome measure was the mean pain score for each condition, as recorded on a 10 cm visual analog scale. The lowest pain scores (mean ± SE) were recorded for the SU and SB conditions at 1.49 ± 0.29 and 1.48 ± 0.26, respectively, and they were significantly lower than the scores for RB (2.34 ± 0.28; P < 0.01) or RU (3.11 ± 0.33; P < 0.001). Each of the slow conditions was reported to be the “least painful” of the four significantly more often than either rapid condition. By this largest blinded study to assess administration rate and the pain of a local anesthetic, the authors found that administration rate had a greater impact on the perceived pain of lidocaine infiltration than buffering (18).

Clinical trials on anakinra (commercially marketed as Kineret, a registered trademark of Swedish Orphan Biovitrum) and related studies in rats demonstrated a correlation between drug concentration, dose level and buffer (19, 20, 21). The vehicle (buffer) and the concentration of anakinra were found to be the cause of mast cell degranulation leading to injection site-related reactions (19, 20). In one of the dose-finding studies with anakinra (21), it was also noted that the injection-site reactions (ISRs) were dose-related. ISRs were experienced by 28% of subjects in the placebo group and by 19%, 38%, 56%, 64%, and 63% in the groups receiving anakinra at 0.04 mg/kg, 0.1 mg/kg, 0.4 mg/kg, 1.0 mg/kg, and 2.0 mg/kg, respectively (19, 21).
These studies also demonstrated that the potential reasons for pain upon injection could be related to the buffer (citrate) at a non-physiological pH (6.5 vs. 7.2) and the presence of the surfactant polysorbate 80 (19). Polysorbate 80, used in the formulation of anakinra, is also present in erythropoietin and has been shown to cause hypersensitivity reactions in patients (22). In another study, tolerability of neutral verses alkaline (pH 10) formulation of human albumin in 10 volunteers was compared. Results are shown in Figure 3. The discomfort associated with alkaline pH, especially when delivered slowly, was more than the neutral pH (23).

**Buffer selection during formulation for reduction or prevention of injection-site pain**

Formulation and the buffers used in the process play an important role in controlling the pain at the injection site, as demonstrated in literature. A histidine buffer is known to be less prone to cause pain upon injection when compared to phosphate and citrate buffers (2, 9, 10, 11, 19). As outlined earlier, a double-blind study of 54 healthy individuals injected with recombinant human growth hormone in two different commercially available solutions (histidine and citrate) with isotonic saline as a reference demonstrated that the formulation using the citrate buffer was more painful to inject than the formulation in the histidine buffer (11). Additionally, as outlined in the randomized, double-blind, crossover study with epoetin alfa, the formulation using a sodium phosphate buffer was associated with less injection-site discomfort and a shorter duration of pain than the formulation containing a citrate buffer (14). These studies (11, 14) demonstrate that histidine and phosphate are better buffers than citrate for subcutaneous formulations.

Buffering strength has also been shown to affect the level of subcutaneous injection-site pain. Since biopharmaceuticals intended for SC injection are commonly formulated at an acidic pH level with a variety of stabilizing agents (4, 5), keeping the buffer strength as low as possible can help avoid pain upon injection (17) since subcutaneous injections occur at a non-physiological pH level. Buffer-free formulations can minimize subcutaneous injection-site pain. Therapeutic proteins require buffering to maintain solution pH, stability, and efficacy while proteins (e.g., antibodies) have their own buffering capacity. MAbs at higher than 50 mg/mL concentrations typically don’t require conventional buffering excipients to control the pH as required at a low concentration (24). Adalimumab (commericially marketed as Humira, a trademark of AbbVie Inc.), was recently reformulated in a citrate-free buffer to minimize the injection-site pain in the treatment of rheumatoid arthritis (25). The mean values of “overall pain at the time of injection” VAS were 6.7 (±2.4) for the existing formulation and 1.6 (±1.7) for the citrate-free formulation, indicating that overall pain at the time of injection was significantly alleviated with the citrate-free formulation (25). Results are shown in Figure 4. The mean values of “pain 10 minutes after injection” VAS were 3.1 (±2.8) for the existing formulation and 0.4 (±0.9) for the citrate-free formulation, indicating that pain 10 minutes after injection was also significantly alleviated with the citrate-free formulation (25).
Injection durations (18) and injection volumes (22) are other measures to reduce injection-site pain. As demonstrated by Scarfone et al. in a single-blinded study with 42 adult volunteers to determine the impact of administration rate and buffering on the pain associated with subcutaneous infiltration of lidocaine, slow administration with a duration of 30 seconds was reported to be less painful than the rapid administration duration of five seconds (18). As reported by Anderson et al., in an open-label, multicenter, randomized comparative study of novel (20 mg/0.5 mL) versus marketed (20 mg/1.0 mL) formulations, the mean immediate VAS total pain score was significantly lower after administration of 20 mg/0.5 mL glatiramer acetate (GA) injection compared with the 20 mg/1.0 mL GA injection. The lower immediate VAS pain score associated with the novel formulation was consistent over all 14 days of the study, indicating that the improvement in injection pain did not diminish over time. The reduced VAS pain score associated with the novel formulation was also evident five minutes post-injection (26). As evidenced by their study, reducing the volume may also provide a moderate benefit. The incidence and severity of local injection site reactions (LISRs) within five minutes and 24 hours post-injection were significantly less for the novel formulation than the marketed formulation. Moreover, even though most patients reported some LISRs following injection of either formulation, a greater percentage of patients treated with the reduced volume solution reported no symptoms within five minutes and 24 hours after injection (26).

Finally, surfactants and excipients may also play a part in increasing or decreasing site pain. Surfactants, such as polysorbate 80, may cause hypersensitive reactions in patients at the site of subcutaneous injection (22), highlighting the fact that polysorbates, which are usually present in protein formulations, need to be controlled properly to prevent hypersensitivity to the drug upon subcutaneous injection. Excipients such as sorbitol can reduce injection-site pain (27) as suggested by large clinical trial studies of Synolvis V-A (hyaluronic acid and sorbitol, Synolvis), a visco-antalgic formulated with 4% sorbitol that demonstrated reduction in injection-site pain (27). The antioxidant effect of sorbitol may also play a role in rapid and strong pain reduction in patients with osteoarthritis, therefore influencing function recovery and medication intake reduction (27). Viscosity-reducing excipients such as amino acids and salt (7) are also expected to reduce injection-site pain due to the injection of a high viscous solution.

Several drugs have been co-formulated with a recombinant protein to minimize injection-site pain due to a large-volume injection. Trastuzumab (commercially marketed as Herceptin SC, a trademark of Roche Genentech) and rituximab (commercially marketed as Rituxan Hycelona, Rituxan SC, and MabThera SC, all trademarks of Roche Genentech) are formulated with the proprietary recombinant human hyaluronidase PH20 enzyme (rHuPH20; Halozyme Therapeutics, San Diego, CA) to overcome administration time and volume barriers associated with existing SC therapeutic formulations. The rHuPH20 works by degrading the glycosaminoglycan hyaluronan (HA), which plays a role in resistance to bulk fluid flow in the SC space, limiting large-volume SC drug delivery, dispersion, and absorption (28).

**Conclusion**

Subcutaneous (SC) injection is a viable alternative for patients requiring frequent treatments because they may be administered by the patient outside of a health care setting. In spite of these advantages, associated injection-site pain is a leading cause of patient noncompliance. The root cause of injection-site pain can be traced back to choices made in the buffering agents, surfactants and other excipients used during drug product (formulation) design. Biopharmaceutical manufacturers may be able to mitigate injection-site pain caused by drug product composition by choosing more appropriate solution conditions to reduce viscosity, pH, and buffering strength in their formulations.

It is well-known that making changes in drug product composition during late-phase development or post-marketing is expensive and comes with a number of regulatory risks. For these reasons, formulators should proactively engage with their chosen chemicals and excipients suppliers early in the process, long before drug product development has been completed and the product composition is locked. Such partnerships between biopharma manufacturers and

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**Figure 4.** Injection site pain for adalimumab at the time of injection and after 10 min. of injection in citrate and citrate-free formulations.

<table>
<thead>
<tr>
<th>Injection site pain</th>
<th>Visual analogue scale (VAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Citrate formulation</td>
</tr>
<tr>
<td>At the time of injection</td>
<td>6.7±2.4</td>
</tr>
<tr>
<td>10 min. after injection</td>
<td>3.1±2.8</td>
</tr>
</tbody>
</table>
chemical suppliers to better identify and, if necessary, develop optimal materials for their product can help ensure drug product development that meets a drug target product profile while improving patient outcomes.

References

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USP Novel Excipients Survey: Stakeholders’ Views on the Current State of Excipient Innovation

Catherine Sheehan, John Giannone, Michael Rashed, Doug Podolsky, and Tanya Mitchell

Survey results indicate that the current regulatory approval pathway for excipients creates a challenge for the use of novel excipients.

Excipients play an essential role in delivering the API to patients and can comprise up to 90% of a medication. As such, excipients are critically important to how well a drug functions in the body. They are also key to advancing a formulation through drug development, according to a new US Pharmacopeia (USP) online survey conducted to better understand how drug formulators view the current state of innovation in excipients and the issues they are experiencing related to new or novel excipients.

FDA has defined a novel excipient as one that has not been used in an FDA-approved drug product and does not have established use in food (1). FDA currently does not review the safety of novel excipients outside the context of an investigational new drug (IND), new drug application (NDA), or biologics license application (BLA) that describes a finished product to which the excipient has been added. Subsequently, drug formulators have encouraged FDA to establish new pathways for the regulatory review of novel excipients. Proponents have said that novel excipients have potential public health benefits such as improved drug delivery or utility in abuse-deterrent opioid formulations (1). Moreover, FDA’s recognition of a novel excipient would reassure drug developers that novel excipients can be used in drug development programs while minimizing the risk that FDA would raise safety concerns during application review.

Partly in response to stakeholder input, FDA announced that it is considering a pilot review program for the toxicological and quality evaluation of novel excipients intended for use in human drugs (1). In light of FDA’s proposal, the survey results highlighted in this article are especially timely.

This article highlights USP’s survey results in key areas concerning limitations created by currently used excipients as well as the reasons these limitations have hampered innovation and led to reformulations, discontinuations, and delays of drugs for the US market. A total of 264 respondents who formulated or supervised the formulation of generics, branded medicines, biologics, or biosimilars during the past five years at companies who manufacture/supply these drugs in the United States or abroad shared their views on the current state of excipients innovation. The overall margin of error of the survey results is +/-6% at a 95% level of confidence.

Challenges

The USP survey indicates that key decisions are made regarding excipient selection across all phases of drug development. However, the current FDA regulatory approval pathway for excipients creates challenges for the use of novel excipients. Currently, use of a novel excipient can potentially risk delays or, even worse, prevent approval for the submitted drug application. Some of the major findings from survey respondents included the following:

- Ninety-one percent of US respondents are familiar with novel excipients compared with 78% of non-US respondents.
- Ninety-six percent said that excipients are at least very important in advancing a formulation through drug development.

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development and provided their reasons, ranging from efficacy to bioavailability (Table I).

- Eighty-four percent said that currently used excipients have imposed limitations on drug development either because FDA-approved drugs in the selected dosage form did not contain the excipient or the formulators were unable to overcome challenges involving stability, bioavailability, or solubility/permeability.
- Seventy-seven percent experienced challenges using novel excipients in advancing formulation through drug development for the US market. Regulatory issues such as acceptance, approvals, and other requirements were the most common challenges (25%); followed by safety (12%); cost, toxicology data needs, and trust factors (10%).
- Eighty-one percent who formulate medicines and who work for suppliers of branded small-molecule drugs or biologics said that drug development has been limited, at least some of the time, due to excipients currently used in approved drugs. The most common reason for this limitation relates to the currently used excipient not being used in the selected dosage form.
- Forty percent felt compelled to reformulate a drug product for the US market because of excipients limitations. For the majority, the delay was one to five years.
- Thirty-one percent said they were somewhat likely and 24% said they were very likely to use novel excipients in the future, assuming no change in the current US regulatory landscape; however, 29% of respondents do not expect to use novel excipients in the next five years, and of those, 43% were respondents from companies with greater than 500 employees.
- Twenty-eight percent experienced a discontinuation of drug development as a result of excipient limitations that occurred the most during the IND and pre-IND phases.

In the USP survey, respondents who work in companies with greater than 500 employees were more likely to experience challenges (84%) than those who work in companies with 500 or fewer employees (67%). More than three quarters of respondents (77%) have experienced challenges using novel excipients in advancing formulation through drug development for the US market. Regulatory issues are the most common challenges (Figure 1).

### Table I. Top reasons excipients are important for advancing formulations through drug development.

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Percent of respondents</th>
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<tbody>
<tr>
<td>Efficacy/quality of drug product</td>
<td>26%</td>
</tr>
<tr>
<td>Stability</td>
<td>23%</td>
</tr>
<tr>
<td>Impact on the formulation</td>
<td>15%</td>
</tr>
<tr>
<td>Impact on drug release</td>
<td>14%</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>10%</td>
</tr>
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</table>

### Figure 1. Challenges respondents experienced using novel excipients.
**Impact of limitations**
The majority of respondents (84%) indicated that currently used excipients have imposed limitations on drug development. Key reasons for these limitations were: excipient not used in an FDA-approved drug in the selected dosage form (54%); unable to maintain stability of final drug product (36%); unable to overcome bioavailability issues (33%); and unable to overcome solubility/permeability issues (32%).

**Reformulations**
Two in five respondents (40%) said they were compelled to reformulate a drug product for the US market because they were limited to using excipients in FDA-approved drugs. Further analysis regarding reformulations highlighted some significant differences. For example, 58% of respondents who manufacture or supply branded small-molecule or biologics reformulated drug products for the US market because they were limited to excipients in FDA-approved drugs. In comparison, only 39% of respondents who do not manufacture or supply such products reported reformulating because of excipient limitations.

**Delays**
For respondents who reformulated a drug product due to limitations, 64% cited the length of delay as one to five years. Survey analysis found that 34% of respondents indicated a delay of less than one year, and 2% said the delay was more than five years. Cross tabulation of results for delays by subgroup (e.g., generic suppliers) found no significant differences.

More than half (57%) cited their inability to formulate a stable delivery of the API as the most common reason for delays, and half (51%) noted their inability to overcome API insolubility or permeability issues.

**Discontinuations**
Due to limitations in currently used excipients, 28% of respondents reported discontinuing a drug’s development for the US market. Of those, 50% of excipient manufacturers and distributors indicated that they had experienced such discontinuations compared to 22% of pharmaceutical manufacturers.

The USP survey results indicated that discontinuation occurred most commonly during the pre-IND phase for 40% of respondents, the IND phase for 37%, and the NDA, abbreviated new drug application (ANDA), or BLA process for the remaining 32%. The most commonly selected reasons for the discontinuation of drug development were:

- Inability to formulate a stable delivery of API with the excipients used in approved drugs on the US market (52%).
- Inability to overcome insolubility or permeability of API using excipients in FDA-approved drugs for the US market (52%).
- Inability to formulate an efficacious dosing level of the API with the excipients used in approved drugs on the US market (48%).

Subgroup analysis regarding these discontinuations highlighted some significant differences. For example, 42% of respondents who manufacture or supply generics or biosimilars were more likely to experience a discontinuation of drug development as a result of excipients limitations compared to 27% of those who do not manufacture or supply generics or biosimilars.

**Advancing formulations through drug development: Expected use of new/novel excipients in the US in the next five years**
Although more than half of respondents (55%) said they expect to use novel excipients in the next five years, assuming no change in the current US regulatory landscape, nearly a third (29%) of the respondents are not likely to use them in the next five years. Importantly, among companies with greater than 500 employees, more than two-fifths (43%) said they are unlikely to use new or novel excipients. This finding supports the exploration of a pathway for review of novel excipients outside of the existing FDA drug application review process.

**Excipients used in drug products approved outside the US**
The survey results also indicated that 44% of respondents used excipients in drug products approved outside the US (i.e., drug products not approved by FDA) for advancing formulations through drug development in the past five years for the US. Moreover, 50% of respondents said they were likely to do so over the next five years. This finding may indicate that the current offerings for excipients permitted for use in US-approved drug products are insufficient to meet the needs of US formulators in drug product development that are critical in facilitating innovation for the advancement of new medical products.

**Excipient manufacturers/distributors vs. pharmaceutical manufacturers**
Cross tabulations of survey results based on organization or company affiliation revealed significant differences between excipient manufacturers/distributors and pharmaceutical manufacturers, including contract manufacturing organizations (CMOs) and contract development and manufacturing organizations (CDMOs). For example, 92% of excipient manufacturers/distributors compared to 82% of pharmaceutical manufacturers said that excipients used in approved drugs in the US limited their ability for drug development for the US market at least some of the time.

In addition, 50% of excipient manufacturers/distributors compared to 22% of pharmaceutical manufacturers said they have experienced a discontinuation of a drug’s development for the US market because they were limited to using excipients used in FDA approved drugs in the US.

**Current regulatory approval pathway for excipients creates challenges**
The USP survey results suggest that the current regulatory approval pathway for excipients creates
challenges, particularly for the use of novel excipients, that has hampered innovation and led to reformulations, discontinuations, and delays of medicines for the US market.

Survey respondents were offered the opportunity to provide additional information and comments regarding their views on novel excipients. The most frequently cited comments were related to regulatory challenges (Figure 2). In addition, some survey respondents provided critical comments on the current state of use of novel excipients (Table II).

FDA’s proposed new pathways

Based on USP’s survey results, USP is supportive of the FDA Federal Register Notice requesting feedback on their proposal to establish a novel excipient review program as it may provide a pathway for review of excipients outside of the existing drug application review process (2). In comments submitted to FDA in January 2020, USP noted that establishing new pathways for the development and regulatory review of novel excipients is critical in facilitating innovation challenges, particularly for the use of novel excipients, that has hampered innovation and led to reformulations, discontinuations, and delays of medicines for the US market.

Survey respondents were offered the opportunity to provide additional information and comments regarding their views on novel excipients. The most frequently cited comments were related to regulatory challenges (Figure 2). In addition, some survey respondents provided critical comments on the current state of use of novel excipients (Table II).

**Table II.** Selected comments from survey respondents on the use of novel excipients.

<table>
<thead>
<tr>
<th>Comment</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>When confronted with the use of a novel excipient, the decision usually is taken to unfortunately avoid its use due to its longer development. It’s an unfortunate decision as novel excipients do provide all round advantages to what exists. We need a regulatory strategy to make the use of new excipients more attractive to the pharmaceutical industry.</td>
<td>39%</td>
</tr>
<tr>
<td>The bar to using a novel excipient is high. It would be helpful if the agencies could more explicitly differentiate between truly new excipients and those which are already used in other products (e.g., foods, consumer products) but are just new to drug product use. I believe the agencies do show some recognition of this distinction in practice, but it would be helpful if they could articulate this as a policy.</td>
<td>22%</td>
</tr>
<tr>
<td>Our experience with the company not willing to take forward the formulation using the two novel excipients is why I respond that it is unlikely that I will use novel excipients under the current regulatory guidelines. If there was a route for regulatory ease or approval for novel excipients that would reduce the risk to our company using novel excipients would reopen the possibility for using novel excipients ... and would probably reopen the project that was killed/reformulated.</td>
<td>8%</td>
</tr>
<tr>
<td>For poorly bioavailable oral small molecules, novel excipients could represent a relatively cost-effective way of performing innovation without having to develop a technology from scratch, as there are really not that many choices of pharmaceutical-grade excipients. More excipients would lead to more drug products and potentially faster approval, which would be in the best interest of patients.</td>
<td>6%</td>
</tr>
<tr>
<td>Regulatory barriers for approval. If the excipient is not already on the FDA inactive ingredients database (IID) or if the intended use is a different route of administration or at a higher level than the IID then the approval challenge has been considered to be too difficult. The second best formulation has been pursued or the project stopped.</td>
<td>5%</td>
</tr>
</tbody>
</table>
for the advancement of new medical products (2).

In its Federal Register Notice, FDA noted that it expects any excipients that undergo complete review would be listed in the Inactive Ingredients Database (IID) after they are used in approved formulations (1). USP continues to support the agency’s efforts to provide a clearer understanding of the information and terminology provided in the IID (2,3). To that end, a USP Excipient Nomenclature Joint Subcommittee (JS) is developing an excipient nomenclature guideline. The JS intends to include standardized approaches for naming complex excipients, including mixtures and polymers in the guideline, and to publish the guideline on USP.org. As recommended by FDA’s guidance on use of IID for single ingredient substances (4), USP proposes using the Global Substances Registration System (GSR5) to promote consistency of the official names for novel excipients evaluated by FDA (2).

USP’s expertise can help address gaps and support innovation
USP has many existing and developing mechanisms to help support FDA’s pilot novel excipient review program. USP’s expertise can help address gaps and support continuous innovation when a novel excipient becomes part of an application for FDA approval. For example, USP can explore how the Pending Monograph Process (5) could be utilized to facilitate development of potential new excipient monographs that are being reviewed as part of an FDA drug application. The resulting monograph could provide identification, compositional, and purity specifications for the novel excipient that coincides with FDA’s review and approval in the associated FDA drug application.

Additionally, USP is working on developing a general information chapter and guidelines that focus on quality information including chemistry, identity, and other specifications for excipients that may also support industry and FDA’s proposal for piloting a novel excipient review program. The availability of standardized identity and naming information for a novel excipient could help the industry and FDA in establishing and evaluating quality specifications for novel excipients very early in the drug development process. Furthermore, a revised USP General Chapter <1074> Excipient Biological Safety Evaluation Guidelines in the United States Pharmacopeia (USP) could potentially help stakeholders by including general information on developing toxicological studies supporting the safety of the novel excipient at anticipated levels and duration of exposure by anticipated routes of administration (6).

By creating standards for excipients, USP’s Excipients Expert Committees play a key role in helping to ensure the quality of the whole medication (7). USP compendial standards provide validated test procedures to establish the identity, purity, and quality of excipients, and USP Reference Standards are authentic specimens that have been tested and approved as suitable for use as comparison standards in United States Pharmacopeia–National Formulary (USP–NF) tests and assays.

Respondent profile and experience
The 264 respondents who qualified for and completed the survey had to have formulated medicines or supervised others who formulated medicines in the past five years at companies that manufacture or supply generic drugs, branded medicines, biologics, and biosimilars. The following list highlights their experience:

- Sixty-four percent worked for organizations that manufacture or supply branded small-molecule drugs; 50% worked for generic small-molecule drug makers/suppliers; 48% for branded biologics makers/suppliers; and 27% for biosimilar makers/suppliers.
- Forty-nine percent worked for pharmaceutical manufacturers; 9% for pharmaceutical contract manufacturing organizations or contract development and manufacturing organizations; 6% for pharmaceutical excipient distributors; 5% in academia; and 4% for pharmaceutical contract research organizations.

- Fifty-nine percent said their company had more than 500 employees, and 41% said their firm had 500 or fewer employees.
- Fifty-eight percent worked in the US, 18% in Europe, 13% in India, and the remaining 12%, elsewhere.
- Twenty-nine percent selected formatter as their primary role; 25% selected R&D scientist, followed by 14% as quality assurance/quality control (QA/QC), and 6% as regulatory affairs manager. The remaining 26% of respondents selected from the roles of academic scientist, consultant, CEO, manufacturing manager, pharmacist, regulatory scientist, medicinal chemist, toxicologist, and other.

- Sixty-five percent selected tablets, injections, and capsules as the dosage forms with most experience. The remaining 35% of respondents selected from among liquids, powders, emulsions, granules, solutions, suspensions, pills, creams, lotions, aerosols, foams, gels, implants, and others.

Summary
The survey results show that the vast majority of respondents who formulate medicines—or supervise others who formulate medicines—reported that drug development had been limited, at least some of the time, due to excipients currently used in FDA-approved drugs. The specific limiting factor noted was that either FDA-approved drugs in the selected dosage form did not contain the excipient or the formulators were unable to overcome challenges involving stability, bioavailability, or...
He notes, “RFID and NFC labels have become more powerful and cheaper in recent years. In addition to the greatly improved reading range of new chip generations in the UHF range, various new functionalities have been integrated, from security to sensor technology.”

A DataMatrix code is the basis for Smart Containers from SCHOTT North America. Laser marking a unique code on the bottom of each vial enables traceability throughout the entire manufacturing process. The unique DataMatrix code is applied during vial manufacturing. After hot forming, advanced laser technologies create the code and inextricably link it to the container. Coded containers may be scanned at various points during the fill/finish process, including after loading, washing, depyrogenation, filling/checkweighing, stoppering, crimping, and labeling, as well as before secondary packaging. “To ensure ease of use, the Smart Container code can be read by conventional camera equipment,” says Diana Löber, global product manager vials at SCHOTT. “Moreover, as the unique identifier is positioned at the bottom of a vial, there is no need to install multiple cameras or to turn the container,” she explains.

Scanning the code supports implementation of Industry 4.0 and helps pharmaceutical manufacturers unlock the power of machine vision and big data analytics by enabling optimal monitoring and traceability of the vial manufacturing and fill/finish processes. “This means that the technology supports and improves reject management and line clearance, reducing the risk of mix-up and optimizing lyophilization processes and container-based targeted recalls,” says Löber.

Caregivers and patients also benefit. With a unique code on each vial, if a product quality problem arises and a recall is necessary, it is easier to identify which vials need to be recalled and remove them more quickly from the marketplace. “This ensures patient safety and high quality up until the drug is administered,” concludes Löber.

For labeled containers, particularly vials and syringes with small radius curves, Schreiner MediPharm offers labels equipped with RFID technology, which relies on...
Edelmann, a folding carton producer, operations

the package without peeling off the seal tamper evidence. Before the seal’s initial
term can be authenticated quickly using
technology prints a small, digital security
product protection. BitSecure copy detection
the cooperation with PragmatIC, we are
mainly been utilized in high-value use
features based on a high-resolution, ran-
dom pattern whose intricate details are
not discernible by the naked eye. The pat-
tern can be authenticated quickly using
a smartphone or handheld reader and analyzed via related software. A closure
seal with an integrated NFC chip and an
irreversible void effect combines analog
digital technologies, offering double
tamper evidence. Before the seal’s initial
opening, the user reads the NFC chip
using a smartphone and related app to
confirm product authenticity. Opening
the package without peeling off the seal
causes it to break along the perforation.

If the NFC chip is read again, the smart-
phone will warn the packaging has been
opened previously. The chip also may
link the user to interactive applications
for patient information and assistance (2).

Sensors for inhaled products
For inhaled products, which are some-
times difficult to dispense correctly, San-
nier and Amiko Digital Health are part-
nering to equip dry powder inhalers with
advanced sensor technology. Amiko’s
Respiro platform tracks device usage in
real-time and facilitates adherence by
ensuring the medication is administered
following the right technique. “Our dig-
ital health tools assist healthcare profes-
sionals and empower patients to achieve
better respiratory treatment results,” said
Duilio Macchi, chief executive officer and
co-founder of Amiko, in a press release (3).

The partners have designed the plastic
part that houses the electronic compo-
nents, completed prototypes, and set the
stage for production. “The engineering
of these plastic parts for serial produc-
tion was quite a challenge,” notes Ursula
Hahn, head of Product Management at
Sanner. Although commercialization is
likely to take some time due to the many
sales channels and stakeholders involved,
Sanner is confident the add-on will be
accepted and successful. In addition,
Hahn predicted, this technology “…will
certainly be transferred to further areas
of application in the near future.”

Another respiratory product partner-
ship, this one between AptaPharma and
Sonmol, an adherence specialist based in
Shanghai, seeks to increase patient engage-
ment and provide better treatment out-
comes for asthma and chronic obstructive
pulmonary disease. The resulting Smart
Inhalers will be marketed primarily in
China and other Asian markets (4).

Blister pack monitoring
One intelligent packaging technology
that’s already commercial is the I-Smart
wallet from Schreiner MediPharm,
which is based on the child-resistant
and tamper-resistant Dosepak carton from
WestRock. A microchip applied to the
blister pack uses NFC to send a signal
to a smartphone to alert the patient to
take his/her medication and monitors
adherence. Janssen Cilag, the winner of
the award in the Equipment Innovation
Category in the International Society
for Pharmaceutical Engineering’s 2019
Facility of the Year Competition, runs
the I-Smart wallet on equipment from

**Beyond packaging**

Smart technologies are not limited to packaging but also can be incorporated
directly on solid dosage forms. One technology from TruTag Technologies adds
an invisible barcode to each pill. It relies on functionalized microparticles of
silica, an FDA-approved pharmaceutical excipient, which forms an invisible,
edible, and high-security optical 3D barcode, known as TruTags. In the case of
tables, TruTags barcodes are added as part of the existing film coat (via stan-
dard pan-coating processes) or applied through an immediate-release clear
topcoat. “TruTags do not impact the release profile or stability of the product
nor do they impact tablet elegance,” reports Dr. Michael Bartholomeusz, CEO
at TruTag Technologies. In the case of capsules, TruTags barcodes are mixed into
existing inks and applied directly on capsules using a standard printing process.

TruTags barcodes can be read by a proprietary, enterprise-level portable
or handheld unit or a mobile phone equipped with a downloadable app.
Bartholomeusz says, “While this phone-based reader can also be used by the
brands and manufacturers, it is especially useful as a consumer tool to ensure
the authenticity of the product … and as a patient interaction tool for the
pharma companies.”

According to Bartholomeusz, “the TruTag solution can bring profound value
to several stakeholder groups — specifically in the area of quality, safety, and
security.” He explains, “For patients, the adoption of TruTags on tablets and
capsules offers a tangible path toward the mass digitalization of medicines
and a future where patients can interact directly with their medicines via cell
phones. The potential value of this interaction has been well-documented and
includes the ability to: ensure patients are getting the correct product in the
correct dosage; communicate prescribing information; monitor and influence
patient adherence; and record adverse events and link them directly to specific
product batches ([for a] risk evaluation and mitigation strategy).”

TruTags barcodes facilitate instant and unequivocal identification of
products anywhere in the supply chain, which is critical when there is a
suspect event. It enables manufacturers and brand owners to determine
whether the problem is related to an internal quality failure, an external
supply chain issue, or third-party criminal actions such as counterfeiting,
diversion, or sale of expired products. Knowing the cause of the problem
allows a pharmaceutical company to take specific corrective action. “While
efforts to serialize packaging certainly help with this process, once tablets
and capsules are removed from their original packaging, serialization is
rendered ineffective,” adds Bartholomeusz. Barcoded tablets or capsules
can be identified throughout the product’s entire lifecycle.

Contin. on page 58
The COVID-19 pandemic has brought increased demand for direct-to-patient trials, challenging cold-chain specialists to become more agile and to strengthen global distribution networks.

The past few years have brought great change to clinical trial logistics, particularly the move to direct-to-patient (DTP) trial models. Increased development of personalized medicines, including gene and cell therapies, has required closer coordination and collaboration between distribution partners to ensure strict delivery timelines and end-to-end temperature controls.

Cold-chain transportation specialists have adapted to these changes, investing in new technologies and programs (Sidebar, p. 48). But in 2020, the COVID-19 pandemic has presented new and unprecedented challenges. Given the strictures of social distancing, demand for DTP shipments increased sharply, at a time when travel bans were in effect around the world, and commercial airlines had stopped a number of commercial shipping routes.

This article highlights some of the approaches that cold-chain specialists are taking to the limits posed by the pandemic. Sharing their insights with Pharmaceutical Technology are Sharon Courtney, logistics services manager for Almac Clinical Services; Alex Guite, vice-president of services and alliances for World Courier; Eric Valentine, vice-president of clinical supply services at Catalent, and Ariette Van Strien, president of Marken.

Pandemic challenges
PharmTech: What are the greatest challenges that the COVID-19 pandemic has posed for your logistics programs?

Van Strien (Marken): Internally, our first real challenge was when the pandemic began was understanding what we would need, globally, in order for our team members to work remotely at all of our sites, knowing that some (e.g. site stafflers, drivers, and warehouse workers) would need to continue to be on-site. We procured laptops and ensured that they were encrypted and made available, quickly. We also optimized scheduling and shifts for efficiency and safety.

Because domestic and international flights and air shipping lanes were interrupted or stopped, we had to choose alternatives. In some cases, we rented our own charters; in other cases, we coordinated with UPS, our parent company, for alternative flight options for Marken shipments through their network. There was also greater immediate demand for DTP services, which required us to address important questions regarding our supply of temperature-controlled plastic shippers and GPS trackers, as well as staff training. We rolled out DTP training, which had already been in place in approximately 57 countries in 2019, to over 80 countries, qualifying local transportation and supply-chain partners.

We also standardized processes, to reduce the customization required for each shipment and customer. For instance, we selected one type of temperature monitoring technology, and one standard approach for handling any temperature excursions. We also focused global locations. For instance, in Asia, we use Singapore as a central location from which to ship products.

Van Strien (Marken): The greatest challenge was ensuring constant communication with investigator sites around the world. Sites often call in the morning requesting service, and normally we would complete shipments by afternoon, but when commercial airlines were down, we couldn’t always arrange things in just a few hours.

Guite (World Courier): Shipping products across international borders has created some logistical hurdles, particularly because certain countries have limited passage to prevent further spread of the virus. In some cases, these challenges have tripled the time it takes to manage a shipment, but we’ve been able to identify alternative routes to ensure that we’re meeting country-specific regulations and preventing delays and temperature excursions.
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Even as commercial flight availability has been reduced, we’ve been able to maintain air connectivity by booking space on airlines across a range of international carriers. This approach allows us to pivot based on the latest conditions and product needs. In fact, through our carrier-agnostic approach and contingency planning, we haven’t declined a single shipment, ensuring that every patient has access to critically needed treatments.

**Valentine (Catalent):** The tightening of international borders, restrictions on travel, and a major reduction in airline capacity and frequency have presented the most significant challenges to the clinical supply chain, affecting both the sourcing of materials and the delivery of medications to patients. From a supply perspective, Catalent has been adding buffer stocks of critical materials and components to protect against the risk of stockouts. We have also seen the supply of some commercial drugs used as comparator products in clinical trials tighten up as manufacturers devote more production time to COVID-19 priorities, as well as individual countries designating existing medications as COVID-19 treatments. In these instances, we are working with our customers to alter their sourcing plans and to ensure that they have a robust strategy and sufficient material to support their ongoing trial needs.

From a distribution perspective, social distancing requirements and significant work restrictions in some countries have impacted our facilities’ processes and workflows. To ensure worker safety, we have realigned several aspects of our operations so that we can be flexible to the changes in our clients’ clinical trials, while also being in a position to rapidly accommodate the needs of clients looking to develop products for the prevention and treatment of COVID-19. For example, due to the restrictions on the number of employees allowed on-site, our Singapore facility has recently moved to a three-shift work force to ensure that we can process all work orders on time, without any impact on ongoing trials.

**Courtney (Almac):** Quarantines, travel restrictions, site closures and limited site personnel are some of the factors contributing to an increased level of risk, presenting complex challenges to those tasked with delivering the right drug to patients, at the right time and at the right temperature.

Changes in patient recruitment levels, study start-up activities, maintenance requirements, and possible changes to the timelines for key protocol milestones are all potential outcomes, as sponsors shift R&D priorities to accommodate the realities posed by the COVID-19 climate. Coupled with this is the level of urgency with which many sponsors are responding to the call to develop vaccines and treatments for the virus.

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**Investments emphasize personalized medicines**

In 2019, cold-chain service providers continued investments in new platforms and services designed for gene and cell therapy clinical studies. Marken opened three new locations in Europe, acquired a logistics firm in Japan, and expanded logistics operations in Philadelphia with a new GMP-compliant plant and liquid nitrogen storage facilities, says president Ariette Van Strien. The company launched a new European Communication Center of Excellence based in Edinburgh to provide consistent communication, monitoring and management to thousands of investigator sites daily, she says. It also opened a new cold chain refrigeration-equipped facility in Dublin, Ireland. In India, Marken’s Direct-to-Patient (DTP) distribution services are now actively delivering to and from 94 cities. DTP shipments had not been permitted prior to the outbreak of COVID-19, but the government now permits this approach, says Van Strien. Marken also introduced Smart Box packaging for temperature-critical shipments.

World Courier introduced a complete cryogenic supply chain, which offers fully automated technology and temperature-controlled transport from the manufacturer’s location to a storage facility and then to each point of care in dry shippers. Through a recent integration with the third-party logistics company ICS, World Courier can charge dry shipments across its network of more than 140 offices and depots, says Alex Guite, vice-president of services and alliances for World Courier.

Before the pandemic, Catalent had introduced solutions designed to enable greater flexibility and responsiveness to change, including demand-led and direct-to-patient supply programs, says Amy Lombardi, group product manager for Catalent’s clinical supply services. The company has been expanding its cold chain capacity for some time, especially in the Asia Pacific region, she says. “In the face of the COVID-19 pandemic, these services have proved to be important tools that customers to adapt their ongoing studies and keep medication flowing to patients, even when they cannot or will not leave their homes to visit a clinical site,” says Lombardi.

Almac made some important changes in 2019, in response to a spike in demand for end-to-end temperature-controlled programs, especially in relation to closing temperature data gaps that often exist at clinical sites, says Sharon Courtney, logistics services manager for Almac clinical services. “Although effectively managing and monitoring temperature during production, storage, and global distribution of clinical supplies can be achieved through appropriate facilities, monitors, and shippers, it’s surprisingly common for temperature data visibility challenges when products arrive at sites. This can be largely due to a reliance on manual data capture that makes accessing records difficult, creating risk and leaving sponsors struggling to identify and adjudicate site-based excursions, assess any trends, maintain compliance and safeguard patients,” says Courtney.

“Historically, clinical distribution has long been considered the global temperature sensitive shipments risk hot spot, due to the multiple third parties that come into contact with drug consignments and the possibility of having temperature-sensitive products held captive in inappropriate conditions during customs checks,” says Courtney. In response, Almac recently launched a new module to its TempEZ platform (Site Storage Temperature Compliance) that plugs the data gap by digitalizing temperature management at site level to increase monitor data upload rates and promote compliance, without adding to the administration burden.

As sponsors grapple with the potential challenges of operating clinical trials in the European Union post Brexit, 2019’s completion of Almac’s new European Campus in Ireland is providing sponsors with certainty and uninterrupted multiple temperatures service provision. This facility is complete with a 79,000 ft² EU Distribution Center and significant storage capacity for 15–25 °C, 2–8 °C, and -20–80 °C temperature ranges, she says.
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PharmTech: What approaches are you using with customers and supply chain partners to improve results?

Van Strien (Marken): We’ve taken a number of steps, e.g. simplifying onboarding for new clients to allow faster program startup. We have also worked closely with all of our clients as the guidelines changed in many countries to allow for adaptive trials, permitting patient home deliveries and Marken’s nursing services to reach patients.

In packaging, we re-forecasted the quantity and types of packaging needed to ship temperature-controlled drugs worldwide as the pandemic spread. Many reusable packaging options had to be moved to single use, but we also increased investment in reusable packaging and temperature monitors to ensure safe delivery around the world, and made sure that the necessary packaging was available in each country in which we operate. Our efforts so far have allowed 80% of staff to work virtually, and prevented any disruption in services.

Guite (World Courier): Recent studies have found that nearly 80% of clinical research study sites have cancelled or put on hold at least one of their current clinical trials. However, now find that many of our customers are seeking new and innovative strategies to support patients who are participating in important clinical trials. We are continuing to collect data to support future therapy development. Since the pandemic began, we’ve seen a five-fold increase in daily DTP shipments.

In these cases, World Courier manages treatment deliveries to, and sample collection from the patient’s home. We have also supplied our drivers with personal protective equipment and implemented a contact-free pick-up and delivery process to protect the health of our associates. We have found that collaboration is key when mobilizing quickly during this fluid environment. That is why it is more important than ever for specialty manufacturers to stay in constant contact with their logistics partners. We are constantly looking at our existing systems to enhance the way we communicate and support customers. For instance, with worldwide flight suspensions, we’ve adapted the technology we use to monitor and manage travel to give our teams more line of sight into scheduling data. This change will allow World Courier’s teams to evaluate schedules from over 950 airlines and provide customers pro-active and accurate information about route mapping.

Valentine (Catalent): One the key changes in demand we have seen during this pandemic is an increase in requests from trial sponsors for clinical site-to-patient (STP) and DTP supply services. It appears that COVID-19 has accelerated the way that clinical trial sponsors, as well as some local regulatory authorities, think about STP and DTP as potential options to support patient needs. It will be interesting to see if the industry and regulations ultimately change to better facilitate adoption of these models beyond the COVID-19 pandemic.

Catalent has had to alter its workflow and processes to accommodate social distancing requirements and protect the safety of our employees, and our partners are facing the same challenges. Open communication with customers has helped ensure we reduce risk in the supply chain. As an example, we recently

What’s Next in Global Transportation

The pandemic has ushered in a period of uncertainty with far-reaching effects. This is particularly true for air cargo. Although COVID-19 created additional need for cargo jets to move new and higher volumes of pharmaceutical products around the world, it drastically reduced the number of passenger jets available to carry that cargo. Temperature-controlled containers are designed to travel in the lower cargo holds of passenger and cargo aircraft. The net reduction in lower hold cargo space reduces the area available to ship pharmaceuticals economically, and creates scarcity that makes shipment planning even more important. Flight reductions in the early days of COVID-19 forced pharmaceutical companies to charter aircraft and plan larger shipments. For temperature-controlled container rental programs, that meant repositioning and conditioning containers quickly to support larger shipping volumes, and required closer coordination between our network stations, pharmaceutical companies, and freight forwarders.

Test kits

Many pharmaceutical companies now find themselves responding to COVID-19 by supporting clinical trials for therapeutics, making testing kits, and supporting vaccine development. The volume of this work is sure to increase as clinical trials grow in number, volume of participants, and global reach. Testing kits present a unique challenge for shipping. Finished test kits are bulky, and current air freight capacity doesn’t support shipping them in significant volumes around the world. Instead, we’re seeing countries import high-quality reagents from South Korea and then manufacturing and packaging the finished test kit in their home regions. These reagents require frozen shipment. They could be shipped cheaply in low-grade packaging made of cardboard, polystyrene, and dry ice. However, there’s a limit to the amount of dry ice that can be safely transported by air, because the material poses a potential asphyxiation risk to the air crew.

Due to decreased air cargo capacity, we’re seeing companies use more efficient packaging with phase-change material with vacuum insulation. The demand for Pelican’s rental products with these materials requires us to reposition many of the containers to South Korea, so they can be used to ship reagents around the world.

What’s next

The impact of reduced flight schedules for airlines may create prolonged industry disruptions that change the way that pharmaceutical companies ship products. It is likely that passenger flight schedules will take significant time to return to 2019 levels, and many airlines are already talking about retiring larger aircraft earlier than planned. This may mean smaller, more fuel-efficient aircraft and less cargo capacity to ship pharmaceutical products. This could push pharmaceutical companies to vary modes of transportation with less reliance on air cargo and diversifying into other modes, such as rail, sea freight, and road.

We may also see scenarios similar to what’s happening with test kits now. Companies could choose to ship products in bulk and use in-country or regional fill and seal, labeling, and packaging contractors to reduce the volume of product shipped by air. Whatever the scenario, it will mean changes for temperature-controlled container rental companies. It will be interesting to see how they adapt to these changes, and how they address their repositioning and network balancing capabilities.

— Dominic Hyde, vice-president of Crēdo on Demand at Pelican BioThermal
Ensuring Integrity of Drug Formulation from Development to QC

ON-DEMAND WEBCAST: Aired Thursday, May 21, 2020

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

Event Overview

After a small molecule has been identified as a viable drug candidate, substantial testing is required to assure that chemical and structural integrity are preserved throughout the drug development process to maintain its functionality. To keep a balance between quality and manufacturability, time-consuming and labor-intensive testing and analysis are required to demonstrate that chemical integrity is intact. Among the techniques used to study changes in chemical integrity are infrared and Raman spectroscopy.

This webcast will discuss where efficiencies can be made in data collection, regulatory compliance, instrument qualification, method validation, and data integrity all along the development pipeline up to final quality control (QC) testing. Learn how to quickly identify changes in polymorphic structure, monitor API to excipient distribution, and troubleshoot out-of-specification (OOS) product lots, while preserving data integrity needed for audits.

Key Learning Objectives

- Where along the drug development path can FTIR, NIR and Raman techniques be used and what knowledge is gained
- How to minimize the number of laborious steps in analytical method validation, verification, and transfer to QC and manufacturing
- What to look for in a hardware-software platform to not only assure drug formulation integrity but also data integrity

Who Should Attend

- Analytical support scientists
- R&D chemists
- Manufacturing engineers
- QC technicians and managers
- Pharmaceutical scientists

Presenters

Katherine Paulsen
Product Manager
— Routine Spectroscopy
Thermo Fisher Scientific

Mike Garry
Sr. Product Manager
— NIR Spectroscopy
Thermo Fisher Scientific

Michael Bradley, Ph.D.
Senior Manager
— Global Training
Thermo Fisher Scientific

Moderator

Rita Peters
Editorial Director
Pharmaceutical Technology

For questions contact Kristen Moore at kmoore@mjhlifesciences.com
had a discussion with one of our suppliers, which needed to alter the processing of heavy shipments in order to safeguard its employees using social distancing. As a result, we are making more frequent shipments in smaller payloads so that multiple workers are no longer required to process an individual container.

Early on in the outbreak, Catalent began an in-depth review of our operations and supply chains, working with our suppliers to consider their supply chains too. That has remained an ongoing process and to date, we have not identified any significant risk, delay, or concern that may have a substantial effect on delivery of any product or clinical trial supplies.

Catalent also formed a multi-disciplinary coronavirus response team made up of senior leaders that reports directly to our CEO. Reaching into all facets of the organization, and continuously monitoring the global situation, this team swiftly executes mitigation activities whenever and wherever they are required.

Quality/Regulations — Contin. from page 43

Solubility/permeability. Reformulation of a drug product was a consequence of excipients limitations, according to two in five respondents. More than one-fourth of respondents experienced a discontinuation of drug development as a result of excipients limitations. More than three-quarters of users have faced challenges in using novel excipients in advancing formulation through drug development for the US market. Regulatory issues represent the most frequently cited challenges, followed distantly by safety concerns. Respondents who work in large companies were more likely to experience challenges using novel excipients. While FDA does not currently review new/novel excipients outside of the drug application review process, it is currently considering a pilot review program for the toxicological and quality evaluation of novel excipients intended for use in human drugs. Based on the survey results, USP is supportive of the recent FDA proposal to explore new pathways for the development and regulatory review of novel excipients.

References

More on excipients

For more on excipients, read the following articles on PharmTech.com:

- Considering Excipient Regulations
  www.pharmtech.com/considering-excipient-regulations
- The Search for Transparency in Excipient Sourcing
  www.pharmtech.com/search-transparency-excipient-sourcing
- Managing Excipient Interactions
  www.pharmtech.com/managing-excipient-interactions
2020 PDA Virtual Annual Meeting

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Bioanalytical studies are an important aspect of biologic drug development that may necessitate partnering with bioanalysis experts.

Bioanalytical studies are an important aspect in biologic drug development because data from these studies are needed to define the characteristics of potential new biologics. Bioanalyses data are also an important inclusion in regulatory filings, driving the need for outsourcing partners with in-depth bioanalytical experience and experience interacting with regulatory authorities.

Pharmaceutical Technology spoke with Robert Kernstock, PhD, director, Immunoassay Laboratory Services at ICON, and Neelanjan Bose, PhD, Director of Bioanalytical Chemistry at Emery Pharma, both contract research organizations (CROs), about the need for bioanalytical testing programs and regulatory strategies for potential new biologics.

Importance of bioanalytical studies
PharmTech: Why is it so important to conduct bioanalytical studies during the development process of a new biologic therapeutic?

Bose (Emery Pharma): Bioanalytical studies, which are designed to provide estimates for concentration of drugs and biologics in pre-clinical and clinic studies of the therapeutic molecule or their metabolites, are critical for various aspects of human clinical pharmacology, studies related to bioavailability (BA)/bioequivalence (BE) evaluation, and some non-clinical studies requiring concentration information for pharmacokinetics, toxicokinetics, or biomarkers. Bioanalytical work serves to supplement pivotal studies and aid in the decision-making process for approval, safety, and/or labeling of a drug or biologic; in short, without proper bioanalytical data, the therapeutic product would not be approved.

Kernstock (ICON): Beyond the regulatory requirements for conducting bioanalytical studies, the scientific importance of the data that these assays generate is invaluable. Bioanalytical assays provide information on certain safety aspects of the therapeutic in determining the maximum tolerated dose. Pharmacokinetic (PK) scientists use the data to determine exposure, half-life, and other pharmacological parameters, which are used to guide decisions on how often and how much of a therapeutic should be given for efficacy without undue toxicity.

Bioanalytical assays extend beyond simply measuring drug concentrations over time but are also used to assess drug efficacy by way of pharmacodynamic (PD) endpoints (i.e., biomarkers). Biomarker assay results may provide early indicators of efficacy, or even safety issues. They can also be used to stratify patients to predict responders or non-responders. Another key bioanalytical assay for biotherapeutics is the assessment of immunogenicity (both wanted and unwanted). For vaccine development, a positive immunogenicity result may be considered to be potential evidence that the vaccine is working as intended. Unwanted immunogenicity is much more complicated as the impact of anti-drug antibodies may influence the pharmacokinetics, efficacy, and safety, and has to be looked at down to the individual patient level.

Regulatory particulars
PharmTech: What type of data/information in particular do global regulatory authorities require from bioanalytical studies?

Kernstock (ICON): For any regulated bioanalytical study to occur, a validated method is required. FDA has issued guidance documents detailing the scope of bioanalytical method validation required for PK/PD endpoints, but it is also important to consider other regional guidance documents (e.g., European Medicines Agency, Pharmaceuticals and Medical Devices Agency [Japan], Agência Nacional de Vigilância Sanitária [Anvisa] [Brazil], etc.) when conducting method validations. The general assessments for method validation consist of accuracy, precision, selectivity/specificity, linearity, robustness, and stability.

Depending on the type of assay, certain parameters may be added or removed to meet the assays’ context-of-use,
Event Overview
In today’s regulatory environment, stricter requirements are being placed on primary packaging components for parenteral drug products. Packaging suppliers are making efforts to meet these requirements in order to ensure their products are accepted by both regulatory bodies and pharmaceutical companies. This webcast will analyze United States Pharmacopeia (USP) General Chapters <381> and <382> and discuss ways to not only meet the regulatory requirements currently in place, but to exceed them with an effort to create a future-proof regulatory pathway.

Topics of discussion will include:
• A review of USP General Chapter <381>, "Elastomeric Components in Injectable Pharmaceutical Product Packaging/Delivery Systems"
• An introduction to USP General Chapter<382>, "Elastomeric Component Functional Suitability in Parenteral Packaging/Delivery Systems"
• A discussion of the best practices for meeting current industry requirements currently for elastomeric primary packaging
• Using industry trends, a look to the future of regulatory requirements for elastomeric components, as well as the presentation of a future-proof strategy to ensure standards are met over time

Key Learning Objectives
• Understand the risks that face the pharmaceutical industry today regarding stricter and evolving regulatory requirements
• Introduce the requirements and understand the implications of USP <381> and <382> for elastomeric components
• Review future trends and how to prepare for regulatory changes over time

Who Should Attend
• Quality/regulatory personnel in parenteral drug delivery
• Formulation scientists and packaging engineers
• Device development engineers and managers
• Technical functions surrounding drug delivery systems
• Extractable and leachable experts
• Procurement professionals

Register for the entire series for free at: http://www.pharmtech.com/pt_p/design_principles

Presenter
Renaud Janssen
Vice-President
Technical Services
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Moderator
Rita Peters
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and the analytical acceptance criteria may also vary. For immunogenicity assays, a statistical report or summary is required to justify your cut point(s). A well-described validation plan detailing the experiments and a priori acceptance criteria should be written and approved resulting in a bioanalytical report summarizing the experiments in tables, descriptions of deviations, and any pertinent conclusions. A quality statement from a quality assurance unit is typically included in the report for any regulated work.

Once the methods are validated, the sample analysis commences that follows bioanalytical plans and/or standard operating procedures (SOPS). The reported data typically contain information on subject (or animal) number, dose/treatment group, time point, and analytical result. A listing of assay performance characteristics, which include tables of assay control results, run summaries, and calibration curve results, are typically provided. Additional information, such as incurred sample reanalysis results and sample condition (e.g., hemolyzed) may also be included.

**Bose (Emery Pharma):** On a broader perspective, FDA requires PK, toxicokinetic, or biomarker concentration evaluation through bioanalytical studies. It is critical that the data are generated via phase-appropriately validated methods (i.e., the methods are ‘fit-for-purpose’) and in many cases adhere to Code of Federal Regulations (CFR), 21, Part 58 (21 CFR 58), Good Laboratory Practice for Nonclinical Laboratory Studies (1). These involve much experimentation, data curation and storage, quality review, personnel training, and generation of SOPs—all related documentation should be available for review by FDA, along with the bioanalytical report.

On a global scale, requirements and expectations around regulated bioanalysis generally follow the same thread as FDA, but with specific regional differences. Most jurisdictions have independent bioanalytical method validation guidance.

**Early development considerations**

**PharmTech:** What types of approaches or strategies are best to plan out early on in the drug development process?

**Bose (Emery Pharma):** Bioanalytical studies are challenging to design and plan properly at the onset of the drug/biologic development process, as they involve samples from multiple pre-clinical species, tissue types, and human-derived samples with a diverse (and in most cases unknown) genetic and metabolic makeup. The bioanalytical methods need to be robust enough to work with the variability that comes with such a diverse set of samples.

It is thus important to anticipate these challenges early on while in the R&D phase, and develop sample preparation protocol(s) and method(s) that can work with such diverse types of samples, varying sample amounts, and be able to account for less-than-ideal sample handling during shipment and storage. It is also preferable to start the method validation process early that ensures that the data are reliable. While FDA guidance suggest that the level of validation should be appropriate for the intended purpose of the study, it is often helpful and cost-effective in the longer term to expand validation a bit beyond that so as to get better prepared for the later development process.

**Kernstock (ICON):** Early in clinical development, it is important to understand the context-of-use for your bioanalytical assays, what type of therapeutic you have, and how your clinical studies are going to evolve. For instance, if you think your lowest effective concentration of your therapeutic is 500 μg/mL (trough levels), then developing an immunogenicity assay that is tolerant to high levels of therapeutic would be a critical consideration early in development. Whether or not your Phase I study is going to be in patients or healthy volunteers is another important consideration.

Similarly, the disease-state biomarker assays may require different sensitivities than if it was in a normal population. Understanding the sensitivity requirements for your PK assay is also important. Intravenous administration of the therapeutic may require a less sensitive assay in serum samples, whereas an ocular injection of the therapeutic will require a very sensitive serum PK assay to measure circulating drug levels. When conducting a preclinical toxicology study, the PK assay may not need a very low limit of quantitation since the therapeutic will be dosed at high(er) levels, and the immunogenicity assay may not have a confirmatory tier as an immune response is expected from a foreign protein. Perhaps you have a novel cell therapy, and a flow cytometer is used to collect ‘cellular kinetics’. This means special handling instructions to analyze the samples within the demonstrated stability window, or the use of additives in the collection tube to stabilize study samples.

**Best practices**

**PharmTech:** Are there any ‘best practices’ procedures or steps you can recommend for beginning a bioanalytical study program for a new therapeutic?

**Kernstock (ICON):** There are a few best practices to consider, including identifying an appropriate blank matrix pool, testing disease-state selectivity as early as possible, and having a good supply of excellent critical reagents identified and appropriately characterized. Addressing these considerations will go a long way to avoiding future analytical headaches. Understanding the mechanism of action of your drug and how it relates to the sample is a critical assessment. For instance, if the drug target is a soluble cytokine that is abundant in serum and plasma, don’t be surprised if your selectivity experiment fails. More importantly in that case, what matrix pool are you using for your standard curve? Is the pool stripped of the cytokine, or did you use a surrogate matrix that doesn’t contain the interfering molecule?

**Bose (Emery Pharma):** FDA’s 2018 guidance on bioanalytical method validation (2) is a great place to start. Additionally, while still in draft form, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) M10 Bioanalytical Method Validation guidance (3) has been a decade-long collaborative initiative of analytical sciences and regulatory agencies around the globe; it is among the best resource currently available to plan for, and design bioanalytical studies.
Editors’ Series:
Strategies for Designing Adaptable, Resilient Bio/Pharma Facilities

ON-DEMAND WEBCAST
Aired: Tuesday, May 26, 2020

Event Overview
Contamination control has always been a leading concern for bio/pharmaceutical facilities and operations. Facility and HVAC design, process workflows, and standard operating procedures for personnel and equipment are all designed to protect the product and people.

The COVID-19 pandemic requires bio/pharma companies to look beyond good manufacturing practices to assess the how the potential spread of the virus may impact different areas of development and manufacturing facilities, employees, visitors, and product.

In this webcast, experts will review strategies for evaluating practices at existing facilities and will discuss options for designing new facilities that can accommodate future needs, including flexibility requirements and any emerging threats.

Topics include the following:

- Moving beyond basic maintenance procedures
- Using airflow modeling and simulation to optimize manufacturing, personnel, and material flow
- Strategies for rapid process scale up, changeovers, and return to full capacity
- Implementing science-based design principles for innovative, affordable facility designs

This Editors’ Series webcast is presented by Pharmaceutical Technology magazine, in conjunction with INTERPHEX.

Who Should Attend
- Managers and project leaders at bio/pharma companies and contract development and manufacturing organizations responsible for facilities, cleanrooms, operations, process development, maintenance, quality control, safety, and personnel.

For questions or concerns, email kmoore@mjhlifesciences.com

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PharmTech: Why is it important, or even necessary, for some biopharma companies to partner with an outsourcing partner for the purpose of bioanalytical studies?

Bose (Emery Pharma): Method development in bioanalytical studies is a black box to many, requiring intense investigation and somewhat intuitive understanding of how analytes behave in diverse biological matrices. It is important to note that, unlike standard analytical studies, bioanalyses involve highly complex and largely undefined biological matrices, with likely millions of compounds that can interfere with specific and accurate concentration evaluation.

The required knowledge and expertise to successfully navigate bioanalytical studies may not be acquired quickly in-house, particularly when the regulatory landscape around bioanalyses changes regularly. Additionally, most bioanalytical studies are moving towards mass spectrometry (MS)-based analyses, which involve instrumentation that is too expensive to acquire for many companies and require specialized training for use and data analyses.

Furthermore, most bioanalytical studies involve conducting the work under good laboratory practice (GLP), thus, the analytical laboratory must adhere to 21 CFR 58. This requires companies having a quality system in place, regular audit of the facility, maintaining documentation, training records, instrument qualification, and so on, all of which often becomes too cumbersome for many biopharma companies with limited operational budget. It is thus much simpler to partner with a CRO with expertise in bioanalyses, which already have an established quality system and the required experience in interaction and data presentation to FDA and other regulatory bodies.

Kernstock (ICON): Partnering with contract laboratories can be extremely beneficial, and there are a number of reasons for doing so. The capacity in your own lab may have been exceeded and the need to outsource work to a partner lab would be necessary. Your own lab may be lacking in certain analytical equipment or experience, and a contract lab would be able to provide that service and expertise. CROs are particularly useful to smaller biotechs as the CROs can provide valuable consulting services and an expanded scope of service offerings such that they can be a ‘one-stop-shop’ for all of your bioanalytical needs. CROs have a very deep understanding of bioanalysis based on the number and diversity of assays they have developed. This is reflected in their scientific expertise as well as their understanding of global regulatory practices, since they are more frequently audited by multiple regulatory agencies; these factors end up benefiting all of their clients.

References
3. ICH, M10 Bioanalytical Method Validation, draft version (Feb. 26, 2019).  

Operations — Contin. from page 45

C-Matic and ECCT. On the line, one machine automates and performs virtually every step in the packaging function. Capable of being remotely controlled, the line is designed to be flexible enough to run a range of dosage forms and blister designs for quick changeover and speedy product launches. The result is shorter cycle times, lower labor and material costs, higher capacity, and enhanced process compliance and reliability (5).

For the patient, medication intake is electronically documented (time and dose). “When the patient pushes a tablet out of the blister, data are generated in real-time, such as the time of removal, the dose or, optionally, the respective cavity,” explains Uwe Braun, product manager of Patient Compliance Monitoring Solutions at Schreiner MediPharm. These data are automatically stored in the package and transmitted to a database via a smartphone app or a reader using NFC or Bluetooth.

For Janssen Cilag, the I-Smart Wallet was customized for its drug. “All electronic features were integrated without any change of the existing package design,” reports Braun. As a result, end-user convenience could be assured because the blister pack use and push-through forces remained unchanged.

Inline readers on I-Smart wallet production lines and pharmaceutical packaging lines verify all functionalities are working before finished packages are released. “Additionally,” Braun says, “specific data such as lot number, ID codes, and medication name can be stored on the chip inside the package. Finally, a full digital track-and-trace system with security features can be added optionally.

The future
Smart packaging will continue to enhance patient safety and counterfeit protection. Hahn predicts, “Track-and-trace will also develop further to ensure a more transparent supply chain.” She also believes demand for integrated smart devices will expand so caregivers and patients will know when a dose was taken and that it was administered correctly.

With technology evolving and prices declining, “We . . . see many opportunities for RFID and NFC labels,” adds Rehm. He predicts, “The possibility of integrating sensor functionalities (temperature, humidity, etc.) will enable a large number of new applications at unit level.”

References
Event Overview

Now that you are starting to see promising clinical results, the focus quickly shifts to commercialization and the many challenges that come from planning a pharmaceutical packaging strategy. In order to be successful, it is critical to consider all packaging design and development requirements including the most cost-effective options regardless of annual product volumes.

Key Learning Objectives

In this webcast, you will learn:

- How to build a robust commercial pharmaceutical packaging strategy for successful commercialization of your product
- How to choose the right pharmaceutical packaging strategy for your project based on product size and growth path
- What the key technical considerations will be in your pharmaceutical packaging design and operational planning

Who Should Attend

- Procurement
- External Sourcing Managers
- Development Project Managers
- Development Scientists
- Packaging Engineers

For questions or concerns, email mdevia@mjhlifesciences.com
Compatibility and flexibility are important
As with any formulation, one of the biggest challenges to developing orally disintegrating/fast-dissolving products is ensuring API-excipient compatibility. “Even though the majority of the excipients are pharmacologically inert, sometimes physical and chemical interactions between the API and excipients can occur that affect the stability, safety, and efficacy of the drug,” Gosden explains.

For fixed-dose combinations involving two or more APIs, the question of whether the APIs are chemically compatible or prone to interact when combined must also be considered. Catalant addresses this issue when using its Zydis technology by using two or more homogenous formulations that are dosed sequentially under different conditions prior to freeze-drying. “This approach addresses issues of incompatible APIs/ingredients in the formulation, yet also may be related to incorporated inactive excipients,” says Gosden.

ODT formulators should also prioritize exploring the relationship between tensile strength, friability, and disintegration, according to Karry. “Tensile strength is lower for ODTs compared to regular tablets due to fact that you need higher porosity for solvent uptake and core hydration. Similarly, disintegration tests are decent in-vitro predictors of palatability as patients prefer dosage forms that do not linger in their mouth for too long,” he adds.

Given the wide range of APIs and the drive to develop more patient-centric formulations including orally disintegrating fast-dissolving products, it is also important for formulators to have access to broadly flexible platform technologies that can be used for multiple drugs, Chandar asserts. “An antiretroviral drug may require a very high dose, while a cardiovascular therapy may need minimal loading. A universal excipient platform that can be used for both types of formulations and generate robust tablets that don’t apart when the patient opens the package dramatically simplifies the process,” he comments.

Chandar goes on to note that excipient technologies that provide rapid dissolution and can also aid in enhancing bioavailability are particularly attractive given that nearly 75% of pipeline candidates fall in BCS Class II or IV. In addition, ODT excipient technologies if designed appropriately may even be able to facilitate the oral delivery of some smaller biologic drugs— notably peptides—by enabling sublingual dosage forms that dissolve under the tongue in just five seconds, avoiding first-pass metabolism in the liver.

References

Manufacturing — Contin. from page 31
Disinfectant formulation. It is important to be aware of and understand the formulation of a disinfectant when applied to a particular surface for consideration about potential residues. Good practice utilizes high quality pharmaceutical-grade water (e.g., water for injection) for dilution of disinfectant concentrate. Following a manufacturer’s label for the volume of water to use when diluting disinfectant concentrate is critical, and any variation can influence the occurrence of residue and performance. Disinfectant stability may be related to incorporated inactive ingredients in the formulation, yet also may influence residue occurrence. Compatibility of the disinfectant on a particular surface is another parameter.

Consider the intended purpose that the disinfectant was formulated to serve. Some cleaning and disinfection products intended for GMP environments may have been originally formulated for clinical or hospital settings that are more commonly highly soiled environments. Although these products are available for use within a cleanroom environment, these products will be formulated to address greater soiling and contamination than would be anticipated in the average pharmaceutical cleanroom. Therefore, it is likely that these types of disinfectants will contain a higher degree of surfactants and actives than are necessary to control and maintain a classified cleanroom; all contribute to the residue profile of the product.

Conclusion
Disinfectant residues pose various risks to the cleanroom environment, which is why the industry and regulatory groups have a renewed focus on the effective removal of their residues. End-users can combat disinfectant residues in many ways, such as implementing a routine residue removal program, instituting “low-residue” disinfectant formulations, and focusing on operator training to control application.

More on cleaning
To read more about cleaning, go to PharmTech.com to read the following:
In addition, the guideline also recommends that, "If the demand for MNPs cannot be met by the measures described above, manufacturers can consider reducing activities that are more directly connected with batch manufacturing or a product accept/reject decision provided that they have a documented rationale or risk assessment to show that the proposed changes will not unacceptably reduce assurance of product quality. Examples include:

- "Not requiring second-person verification of activities for less critical steps (though we recommend a self-check of work)
- "Reducing the number of samples for labor-intensive laboratory testing
- "Forgoing an in-process test to assure adequacy of mix, particularly when making successive batches, where the risk is judged to be low in terms of drug safety and efficacy
- "Delaying completion of deviation investigations of minor events.

"CDER [the Center for Drug Evaluation and Research] recommends that in taking such measures, firms plan to carefully monitor indicators of product quality to note any unfavorable trends or shifts as a result of the implementation of the Plan. CDER also recommends that firms retain samples for testing at a later date in cases where testing is reduced or omitted because of lack of resources" (2).

While it is important to act quickly and efficiently during a crisis, the process and product must still be manufactured in accordance with appropriate regulatory requirements. Before you make any drastic changes to SOPs or eliminate process steps you need to read the FDA guidance document, prepare a proper risk assessment, and justify why the removal of the requirement from the SOP does not impact patient safety and product quality. The documentation you provide and the assessments you perform to address some of the extraordinary situations facing you and your colleagues in the effort to produce necessary medical drugs should give you confidence that you have acted appropriately and within the regulations to fulfill patient needs.

References

Following Guidelines During a Crisis

Products must be manufactured in accordance with appropriate regulatory requirements, even during a pandemic, says Susan J. Schniepp, executive vice-president of post-approval pharma and distinguished fellow, Regulatory Compliance Associates.

Q. I am in the quality department and am responsible for investigations, and I have been working from home due to the COVID-19 pandemic. The investigation standard operating procedure (SOP) requires me to perform face-to-face interviews with people and to complete the investigation within 90 days. Working remotely to conduct the interviews is taking much longer, and I am afraid I’ll miss my deadlines. Could I eliminate the interview requirement until I am able to return to the facility?

A. I certainly understand the challenges of trying to conduct remote face-to-face interviews and the need to try and streamline processes during times of crisis, but now is not the time to take unnecessary, undocumented shortcuts with any of your procedures. My recommendation is that you step back from your frustration with the situation. Focus on the elements you need to conduct a thorough investigation and look at finding alternative means to fulfill the SOP requirements as defined in your contingency plan. If you do not have a contingency plan in place, you should immediately develop one and include appropriate risk-based information. The European Medicines Agency has a guidance on the format for a risk management plan that might help you get started on this activity (1).

To determine how you might make your operations more efficient during crisis times, I further suggest you review the FDA’s draft guidance titled, Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products (2). The guidance document states, “This guidance is intended to encourage manufacturers of medically necessary drug products (MNP)s and any components of those products to develop contingency production plans to use during emergencies that result in high absenteeism at production facilities” … “The guidance provides considerations for the development and implementation of a plan for production of MNPsl during a crisis, including specific elements that should be included in the plan.”

The contingency plan you develop should include information regarding the company’s prevention and risk mitigation processes. The guidance states, “These preventative measures can include steps to prepare personnel such as:

- “Educating employees on topics such as, in the case of a pandemic, personal hygiene (hand washing and coughing and sneezing etiquette), social distancing, and appropriate use of sick leave
- “Encouraging employees to get immunized as appropriate by providing information on local vaccination services or by offering on-site vaccination services, if reasonable
- “Providing information for and encouraging employees to develop family emergency preparedness plans
- “Reviewing CGMP [current good manufacturing practice] regulations regarding appropriate sanitation practices and restriction of ill or sick employees from production areas (see 21 CFR [Code of Federal Regulations] 211.28)” (2).

The contingency plan you develop should include information regarding the company’s prevention and risk mitigation processes.

The guideline also recommends “that manufacturers, when evaluating activities that might be reduced in frequency, delayed, or substituted by a suitable alternative, first identify and consider activities that are intended by the CGMP regulations to provide controls not connected with the manufacturing of any specific batch. Examples include:

- “Production equipment routine maintenance
- “Utility system performance checks and maintenance (e.g., air temperature, lighting, compressed air)
- “Environmental monitoring of facilities such as cell culture, harvesting, and purification rooms during production
- “Stability testing for certain drug products and components
- “Periodic examinations of data and of reserve samples” (2).

Contin. on page 61
European Pharmacopoeia

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