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A s editor of a publication for bio/pharmaceutical development, I spend a lot of time reading about the latest drug development trends; one emerging theme is patient-centric drug design.

That topic came to mind as I experienced the trials and tribulations of dealing with a recent bout of flu-like symptoms (despite getting a flu shot). For example, attempting to match symptoms to the hundreds of over-the-counter (OTC) medicines in the drug store aisle was a dizzying task, especially while ill. Difficult-to-open packages, blister packs that did not list expiration dates, and confusing dosing instructions contributed to my frustration. And the prescription and OTC medicines I took literally left a bad taste in my mouth.

While my illness was routine and I soon recovered, the implications for patients with serious medical conditions who do not adhere to complex dosing regimens can be health- or life-threatening. Therapies that require multiple oral doses per day, painful injections, administration by trained medical professionals, or have adverse side effects are just a few challenges to effective dosing of drugs. Physical limitations, such as problems swallowing, also complicate delivery of the drug.

In the cover story for this issue, formulation experts discuss the need to bring the patient’s experience to the forefront of drug formulation strategies. Development strategies should include more than just studying the biopharmaceutical and physicochemical characteristics of a drug molecule. Understanding the patient’s physical and dosing needs at early stages of development will be crucial.

I will moderate a panel discussion on patient-centric drug design at CPhI North America in Chicago on April 30, 2019. See the CPhI North America Planning Guide in the accompanying Pharmaceutical Technology solid dosage supplement or visit www.cphinorthamerica.com for more information.

Controlling infectious diseases

While I cannot confirm where I picked up the virus that made me sick, I stayed home for a week to contain the illness. Practical measures such as isolation of an infected person and vaccinations can help contain disease outbreaks.

The Centers for Disease Control (CDC) (1) estimates that 31–36 million people experienced seasonal flu illnesses in the 2018–2019 flu season, prompting an estimated 16.8 million doctor visits, a half million hospitalizations, and up to 46,800 deaths. Based on CDC estimates, the 2018–2019 season was the second most severe in the number of illnesses and doctor visits, fifth in hospitalizations, and fourth in deaths, when compared with other flu seasons dating back to 2010. And, an estimated 169.1 million doses of flu vaccine were distributed in 2018–2019, an increase of almost 9% over the previous season (2).

While measles was declared eliminated from the United States in 2000, reported cases spiked in 2019. Through mid-March, the CDC reported more than 300 confirmed cases of the disease in 15 states, up from 17 cases in 2018. The outbreak was attributed to international travelers bringing the disease to the United States as well as clusters of unvaccinated people in certain communities.

An outbreak in Rockland County, New York prompted county officials to declare a state of emergency that barred anyone under age 18 who was not vaccinated against the measles from public places for 30 days or until they receive a vaccination (3).

Officials told media outlets the measures were taken to get the public’s attention and encourage more vaccinations. Backlash against the emergency order illustrated that opinions about a patient’s (or parent’s) right to refuse treatment are strong and present another medical treatment challenge.

References
2. CDC, Measles Cases and Outbreaks, www.cdc.gov/measles/cases-outbreaks.html
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These references are produced under the company’s ISO 17025:2005 laboratory accreditation and ISO/IEC 17034:2006 reference material producer accreditation. They will also comply with the newest revisions of United States Pharmacopeia General Chapters <854> and <1854> on MidIR spectroscopy.

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The instrument is supported by SECview software, which streamlines the calculations required by the advanced detectors and performs analysis of sample-of-interest using multiple calibration methods simultaneously. The software is capable of gel permeation chromatography system/hardware control, multi-channel data acquisition, data processing, and analysis.

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Continuous Manufacturing Gains Major Push from FDA

Jill Wechsler

FDA is moving to shift industry away from step-wise batch production.

Regulatory authorities in the United States and other regions are encouraging investment in continuous manufacturing (CM) processes to better ensure quality drug production, avoid shortages, and ultimately lower the cost of medications for patients. The aim is to support an industry shift away from step-wise batch production, which is vulnerable to contamination, errors, and stoppages, to the use of automated modular systems better able to reduce human error, waste, and delays.

As of January 2019, FDA has approved five products from four manufacturers that use CM systems. These involve small molecules, but more comprehensive CM processes are in development for proteins and biologics. FDA reports that approximately 20 companies—both brand and generic—are talking to agency staff about developing and implementing CM processes.

To spur more manufacturers to join the trend, FDA published new draft guidance in February 2019 that clarifies its policy regarding CM approaches (1). The aim is to address manufacturer concerns that adoption of CM technology could delay approval of new drug applications or complicate switching from a batch to a CM process for marketed products, explained then FDA commissioner Scott Gottlieb and Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), in a statement highlighting agency efforts to expand industry investment in modern manufacturing systems (2).

The new guidance provides advice on what process and control strategy designs, including equipment, are needed to meet regulatory considerations. The guidance applies to CM for drug substances of all finished dosage forms, including drugs, generic drugs, and over-the-counter products, but not to biologics. It aims to clarify definitions of batches, process validation, and quality systems considerations for CM and to provide recommendations for scaling up production and demonstrating stability for finished drugs produced with CM systems.

To overcome company concerns about the cost of investing in new production technologies, FDA emphasizes that CM platform technology can be used to manufacture multiple products, which can help reduce the risk of drug shortages and facilitate scale-up of production when needed. An added benefit is the smaller footprint for CM systems, along with greater efficiency and consistency in these operations.

Gottlieb and Woodcock also cite increased FDA funding for private organizations assessing CM technology in laboratories, as well as support for internal agency investigation of CM and other technologies. CDER’s Emerging Technology Team (ETT) also is providing additional help for early adopters of CM in implementing new technology and navigating the application review process for products made with these modern methods. Additional funds in FDA’s 2019 budget will support further development of a standard operating approach for CM and advanced manufacturing, with the overall aim of reducing dependence on the import of pharmaceutical ingredients and products to better assure quality and supply.

At the same time, the International Council for Harmonization (ICH) is moving forward to establish standards for continuous manufacturing of drug substances and drug products, with the aim of developing a common framework for regulating and approving products that utilize CM methods. ICH approved a concept paper on the topic at its November 2018 meeting, and a panel of experts is mapping plans for developing a new quality guideline (Q13) on this topic. The aim is to establish common definitions for CM, articulate key scientific issues, and harmonize regulatory concepts and expectations across the regions. Participants hope to complete the project by the end of 2021, after conducting a series of site visits to CM facilities for both small and large molecules and learning more about state-of-the-art technologies. The expert working group includes representatives of industry and regulatory authorities in the United States, Europe, Japan, Canada, China, Korea, Singapore, and other nations.

Bringing in biologics

While most CM operations so far have involved small molecules, manufacturers of biologics also are assessing how
CM may apply to both upstream and downstream biotech production. This topic was examined in depth at the January 2019 CMC Strategy Forum on Continuous Manufacturing for Biologics organized by CASSS (3). Industry experts discussed advances in implementing CM for small molecules, noting that adoption of this approach in biomanufacturing has been limited largely to upstream “hybrid” approaches. BioMarin Pharmaceutical vice-president, Novato Operations, Erik Fouts noted that equipment manufacturers are offering small and pilot-scale CM systems for integrated continuous upstream and downstream processes and that these approaches are drawing interest as ways to boost productivity, lower the manufacturing footprint, and avoid waste in raw materials.

Participants at the Forum supported the ICH effort to develop the Q-13 guideline on CM as important in encouraging flexible approaches for implementing CM in manufacture of small molecules and therapeutic proteins. The aim is to clarify regulatory concepts, such as batch, process validation, and continuous process verification. While CM has the potential to increase flexibility and robustness in biomanufacturing, and to reduce costs and product heterogeneity, challenges remain in assuring sterility and advancing process controls.

These issues were addressed more broadly at the CASSS WCBP 2019 Scientific Program (4). The three-day program concluded with a review of initiatives to achieve flexible and modular facilities and the use of process analytical technology (PAT) in continuous manufacturing. PAT for an integrated continuous biomanufacturing platform is “becoming a reality today,” the experts concluded, noting that there remain many questions to consider in the journey to flexible and modular facilities.

References
Patient-Centric Drug Development Comes of Age

Felicity Thomas

Easier access to information, targeting smaller patient populations, and increased regulatory focus on patient outcomes are driving patient-centric drug development.

In light of the fact that patients are generally becoming more informed, with immediate access to information for many, it is unsurprising that bio/pharma companies' approaches to drug development are shifting. Factoring in the trend toward targeting niche disease areas and increasing focus of regulatory bodies on patient experiences, patient-centric drug development becomes an apparent inevitability.

"Whilst the need for patient centricity has always existed, the focus on it has never been greater," explains Ronak Savla, scientific affairs manager, Catalent Pharma Solutions. “Every dose design decision during development has the potential to influence patient outcomes. Besides safety and efficacy, patient-centricity should be the foundation of creating a target product profile.”

Agreeing with Savla, Stewart Griffiths, product commercialization manager, 3M Drug Delivery Systems Division, adds, “Nowadays, patients expect to be more involved in managing their own health. We live in a world of empowered patients, who are better informed thanks to digital media and the Internet.”

The incentive for companies to focus on and involve the patient during drug development is that the end product is more easily accepted and used by the patient, Griffiths further explains. If issues surrounding the use of different treatments and therapies can be overcome then the likelihood of market success should be increased, he states.

“Patients, along with providers and payers, are demanding more holistic health solutions,” says Michael Dennis, director, operations science and technology, AbbVie. “Thinking through product design, development, and lifecycle can translate into better patient experiences, compliance, and adherence. This includes defining, at the earliest stage possible, the quality target product profiles (QTPPs) and critical quality attributes (CQAs) to ensure the safety and effectiveness of the new drug product,” adds Bill Huang Sr., principal research scientist, formulation sciences, AbbVie.

Therapeutic value and the importance of adherence

“It’s important to understand as early as possible which approaches will offer the most therapeutic value to patients, and that includes the proposed compound’s path to treatment..."
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and dosing regimens,” notes Kim Zubris, formulation director, Particle Sciences. “Obtaining desired or required bioavailability in pursuit of therapeutic targets begins in formulation and often involves addressing issues related to dose concentration, form, and administration routes including oral solids and liquids, inhalants, intravenous, long-acting injectables, and topically administered medications.”

An analysis performed by the Catalent Applied Drug Delivery Institute, which looked at new drug approvals since 2009, revealed that approximately two-thirds of the drugs were not ‘outcomes-optimized’, in terms of API-wasting formulations, addressable side effects, low bioavailability, and regimen complexity, among other factors that should have been considered, reveals Savla. “Combining the biopharmaceutical and physicochemical knowledge of a drug molecule with how it impacts the patient’s experience should be undertaken early,” he says.

There is tremendous onus on the patient to take the medication correctly—the right amount, at the right time, in the right way—to ensure it is effective, confirms Torkel Gren, senior director, science and technology officer at Recipharm. “It is fairly common for patients to forget to take medicine, a study from 2012 (1) suggests that more than 60% of the patients forget to take their medication,” he continues.

“There are a lot of opportunities to improve adherence by offering better drug products, which pose less development expense than that of new chemical entities. As such, patient-centric formulation is an area where bio/pharma companies can get the best cost-efficiency during development.”

Essentially, however, patients do not want to be reminded they are patients, asserts Savla. “The persistence level for most chronic therapies continues to decrease after three months (2), and can be as low as 30% just two years after starting a medication,” he says. “Adherence rates are inversely correlated with dosing frequency (3). Whereas once or twice daily doses are acceptable, there is a drastic drop in adherence for three-times-daily dosing (4). The use of modified-release technologies can reduce dosing frequency and may improve side effect profiles. Poorly soluble drugs, especially those indicated for cancers, can have high doses in the hundreds of milligrams range that require the patient to take multiple or large dosage units, which can be difficult to swallow.”

Zubris concurs that medication inconvenience being linked to poor adherence is well documented. “The therapeutic value and health benefits of a drug compound can only be realized if patients follow the course of treatment properly. Ease of administration and fewer negative side effects are just a few of the more critical aspects of formulation that drug developers need consider for good patient compliance,” she notes. “Minimizing or eliminating the pain involved in administering the effective dose, as well as minimizing the number of dosing events in the first place, ensure that a drug is easier for a patient to deal with.”

A robust formulation design can minimize pill burden as well as mask unpleasant taste, improve swallowability, and minimize side effects, adds Huang. “The optimal dosage form can make all the difference in whether patients will consistently comply with administration instructions,” he says.

Delivering the goods
During formulation and development, some of the delivery issues facing bio/pharma companies include solubility, stability, and poor gastro-intestinal absorption of the drug molecules, states Dennis. “Additionally, we face problems with highly potent and/or toxic drugs requiring higher quality, in terms of purity and uniformity, and greater patient monitoring and compliance. Or novel molecular combinations requiring complex manufacturing controls,” he adds.

Drug targeting to the diseased area and absorption window can be employed to maximize drug efficacy and minimize adverse effects, Huang continues, which is often built into the formulation design. “Various enabling technologies help drug makers address delivery challenges, depending on the physicochemical properties of the drug substance,” he says.

Poor aqueous solubility can severely limit the usefulness of an API and the ability to dose these molecules in traditional forms, explains Zubris. “Without exploring alternative formulation techniques, these actives may not progress through the development pipeline,” she confirms.

Effective dosing methods for more complex molecules are certainly less straightforward to determine, however, there are several techniques available that can help in these cases. For example, amorphous solid dispersions are now commonly being used for poorly soluble compounds to improve bioavailability without compromising drug product stability. Hot melt extrusion and spray drying have proven to be promising techniques for the preparation of amorphous solid dispersions,” Huang reveals. “Sometimes, more complex oral formulation approaches are selected, such as multilayer tablets and multiparticulates, to modulate drug release profiles, improve drug stability, reduce food effects, and so on. Parenteral injectable delivery systems are often considered for large molecule biologics and some small molecules with poor oral absorption—for which more patient-centric long-acting intramuscular or subcutaneous injectable are considered to reduce the dosing frequency.”
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Drug delivery devices can also help with effective disease treatment and management. “Drug-eluting devices, long-acting depots, and transdermal patches can combine anatomical specificity with API uptake considerations and are proving highly effective at treating disease effectively,” adds Zubris. “Divorcing the patient from actively administering dose after dose at precise intervals is inherently patient-centric.”

For Griffiths, ease-of-use of the delivery device is particularly important for patient engagement. "If you design with the end in mind, by developing a device that is easier to use, patients are more likely to adopt and take on that new therapy,” he says.

Using inhalation therapy as an example, Griffiths reveals that there is a trend being witnessed by the industry towards connected devices. “Technology has a major part to play,” he notes. "A connected device can send reminders to a patient to help with adherence, for example, and also has the potential to help improve technique by providing feedback to a patient about errors in use.”

Packaging also has its part to play in improving adherence rates, according to Gren. “Development of new packages that are easy to open or transport can help,” he says. “Injectable dosage forms may not be considered to be patient centric as they are often seen as an impractical and expensive way of administering drugs. However, in some cases parenteral depot formulations are an excellent way to ensure that the right dosage is always delivered to the patient. Making injectable formulations more patient-friendly will be a focus going forward.”

**Bye-bye blockbuster?**

New drug development was buoyant in 2018 with an increased level of new drug applications, many of which were in the orphan drug category, states Zubris. “At the same time, regulators are providing better drug development economies for therapies in certain preferred categories, assigning special regulatory considerations to speed up their approval process,” she says.

Gren highlights that even though the prospect of developing new drugs for huge markets is still attractive, it has become quite challenging to achieve. “For many of the big disease areas, there are already reasonably good pharmaceutical products on the market, and it is often difficult to come up with something that is significantly better and of course the competition is fierce in these areas,” he adds. “Going for smaller markets and focusing on the needs of smaller patient groups, requires reduced R&D expenses and the chances of success are significantly higher.”

Additionally, the focus on smaller patient groups is prompting drug innovators to integrate patient-centric principles and introduce them at the earliest stages of drug development, asserts Zubris. “This strategy will ensure pharma companies can develop new, more effective drugs faster while improving their therapeutic value with formulations and forms that treat disease more efficiently,” she explains.

Furthermore, Savla points out that many of the smaller patient populations with orphan diseases are more likely to include members of patient advocacy groups and generally have a better understanding of their condition, which means that patient-centric approaches are beneficial in the development process. “Involvement of these patients is more frequently an integral part of the drug development process,” he confirms. “Also, for more niche disease areas, developers may need to tackle unique administration challenges, such as a reliance on caregivers to administer drugs. Therefore, pharma companies need to more strongly focus their efforts on improving outcomes not only by maximizing the efficacy and safety, but also the patient’s experience.”

The decline of the ‘blockbuster’ could be seen as a promising shift as it may lead to companies developing existing drugs into more patient-friendly options, according to Griffiths. “We’ve got some well-established molecules that have been around for decades that are still big sellers, and now we’re looking at how we can improve those products,” he states.

**Considering patient populations**

“Patient-centricity is a universal concept that benefits all patients. Geriatric and pediatric patients, in general, have the potential to be the biggest populations to benefit from more patient-friendly dosage forms,” emphasizes Savla. “However, a drug designed to be patient-centric for one group of patients does not necessarily extrapolate across different patient populations.”

In Gren’s opinion, geriatrics represent the most important patient population to consider for patient-centric dosage forms, as it is the group of patients where non-compliance is most common. “For geriatric patients, it is common to need multiple medications each day, which can make dosing more complicated and in fact, more difficult to remember,” he says. “By introducing extended-release medicines, the number of dosing occasions could be reduced, and fixed-dose combinations could reduce the number of tablets required on these occasions. Dosage forms that are easier to swallow and packets that are easier to open would also be appreciated by elderly patient populations.”

Dennis and Huang, while also highlighting geriatric patients, make note of cancer patients too, who may have issues with administration frequency, pill burden, side effects, or compliance. “Understanding the nature of what these populations are facing can lead to better decisions in formulating therapies that meet their needs,” Dennis adds.

For pediatrics, there was general agreement that most conventional
drug delivery systems are not ideal. “Pediatrics differ in their developmental status and dosing requirements from other subsets of the general population,” stresses Huang. “Different formulation designs are required to aid the development of age-appropriate medicines to maximize patient acceptability, while maintaining safety, efficacy, accessibility, and affordability.”

**Regulatory input**

An important aspect of drug development is in the form of regulatory guidance and standards that need to be met in order for a product to be accepted and authorized for commercialization. In terms of more patient-centricity, regulatory bodies and healthcare providers are also shifting their approaches.

“There’s much more emphasis now to include a structured, scientific human factors program as part of any new device that is being developed,” notes Griffiths. “The introduction of regulatory guidance and standards mean that developers of new products need to confirm that their design is easily used by the patient population without significant use errors. It is expected that a human factors program will inform design changes to a product based upon feedback from real patients.”

Dennis and Huang highlight the example of the draft guidance issued by FDA in the United States, under the 21st Century Cares Act, which states, in part, that sampling methods during development should be used “for collecting information on the patient experience that is representative of the intended population to inform the development” of medicinal products (5). “Both FDA and the European Medicines Agency are focused on how best to assess the patient experience, and therefore are expecting more patient-reported outcomes (PRO) in clinical trials as this assesses outcomes that are important to patients, not just doctors and regulators,” Dennis says.

Further regulatory change noted by Savla is the Research to Accelerate Cures and Equity (RACE) for Children Act (6). “This act eliminates orphan exemption from pediatric studies for cancer drugs directed at relevant molecular targets,” he confirms. “The law will come into effect on Aug. 18, 2020. As a result, many pediatric oncologists and pharma companies are gearing up for more studies of oncology drugs for children.”

**Better dialogue, better treatment**

“Pharmaceutical companies are being urged to develop more patient-centric drug products by various stakeholders, including not only the patients, but also the caregivers, payers, and regulatory bodies,” states Dennis. “Seeking to incorporate the voice of the patients into drug discovery and development is becoming more and more common and important.”

Further improvement in stakeholder engagement and dialogue by bio/pharma companies is expected by Griffiths to not only inform new product design, but also solicit feedback about how to improve existing products. “As a result, I think we will see a continued move toward connected health. Patients want to be more involved in managing their own health, and they want to have user-friendly devices,” he notes. “However, we also need to remember that, while technology moves at a very fast rate in the outside world, the adoption of that technology into pharmaceutical products is very slow by comparison. Both pharmaceutical companies and the agencies that regulate them are on a learning curve, and within a highly regulated industry with patient safety at the forefront, it’s easy to understand why adoption is going to be slower.”

Dennis and Huang agree that digital technologies and artificial intelligence will be transformative in bio/pharma, providing the basis for more patient-centric innovation. “We also believe individualized medicine will continue to be a market driver, and that pharma will be more effective in targeting disease and targeting delivery for specific, localized disease,” Huang says.

Small patient groups will continue to trend for bio/pharma companies in Gren’s opinion, although he also stresses that manufacturing smaller batches may also lead to increases in cost. “The most logical way to achieve affordability is to consider the costs of raw materials, manufacturing, and quality control early on in the development phase. This, of course, requires development scientists with a good understanding of industrial-scale manufacturing,” he says. “The cost of goods may also be limited by using intermediates that can be used for different products.”

However, Gren remarks on the impressive level of creativity that is being shown in terms of patient-centric development. “To me it seems like many of the best ideas are realized when experience and insight into healthcare and patient needs are combined with in depth knowledge of pharmaceutical technology,” he summarizes.

**References**

The presence of the probable carcinogens N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) found in APIs used for the production of a number of generic versions of angiotensin II receptor blocker (ARB) medicines has raised concerns about how manufacturers and regulatory bodies address the potential for production of undesirable impurities (1). The products in question complied with regulations yet contained genotoxic compounds. FDA has taken several steps to address this particular issue (2,3). Drug makers also clearly need to consider what approaches they should be taking to ensure their API suppliers are supplying high-quality material that is safe for use in final drug formulations.

“Despite the fact that manufacturers have the process knowledge and experience that regulatory bodies do not have, we are still dealing with massive recalls of very important medications, the scope of which just keeps increasing,” observes Macniell Esua, chief compliance officer at CordenPharma International. In this particular case, Esua points out that it appears that a trace impurity in a solvent reacted with a process reagent used, resulting in a genotoxic impurity. “Surprising levels of the impurity are being found in the drug that exceed the levels one might have predicted and that are allowed. One guess is that recycled solvents may be a contributing factor,” he notes. Esua adds that it is critical that the full investigation findings be shared with the industry in an open fashion, so everyone can learn from this potentially tragic situation.

Value of fate and purge studies
During a process validation exercise related to an investigational new drug, a full fate and purge study should normally be conducted, according to Esua. In the current situation with valsartan and related products, Esua suggests a fate and purge study would have correctly identified NDMA as a potential impurity in the process. “As a result, work would have been conducted to identify the potential risk of introduction of NDMA in the final product and to develop mitigation strategies. Through the change control process, full consideration should have been given to the change in solvent, the potential impurities that the change was introducing, and the downstream implications,” he says. He also points out that this issue is again related to the scientific competence aspect—and whether the study was conducted with sufficient rigor or paid “mere lip-service.”

Looking specifically at the issues concerning valsartan, it is also important to note that after the initial recall of drug product containing an API manufactured by Zhejiang Huahai China, additional API manufacturers in China and India had their approvals recalled for the same reason. “The presence of nitrosamines is not only a ‘variation’ problem but has also been shown to be a GMP cross-contamination problem at some of the manufacturing sites involved,” says Rolf Arndt, senior quality assurance and regulatory affairs specialist with Cambrex.

He adds that the fact that different nitrosamines were identified for both APIs and drug products makes the problem more challenging, because the required maximum specification limits of nitrosamines are substantially lower than for normal impurities.

“The issue is not a simple question of ‘approval systems,’ but more a combination of better evaluation of the risks of formation of nitrosamines as well as better analytical techniques; but most importantly, that API manufacturers have sufficient controls within their GMP procedures to avoid cross contamination,” Rolf asserts. “Furthermore,” he states, “because this field is so fast moving, it is not enough to merely comply with the regulations; it is important to be ahead of them.”
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Risk assessments essential
Any process change must involve a risk assessment that includes a judgement of whether the proposed changes have the potential to result in the production of new or additional impurities, according to Arndt. The assessment should also identify whether there is a risk of formation of impurities that may fall under International Council for Harmonisation M7 guidelines.

“If there is a risk of formation of so-called ‘M7 impurities,’ further investigation must be performed, and the basis to exclude any process change must rest fully on supportive analytical data,” Arndt states. “These types of impurities cannot normally be detected by simple chromatographic methods that are used for ‘related substances’—substances similar to the API, so more advanced techniques must be used, for example, tandem mass spectrometry MS/MS,” he adds.

Burden rests with the manufacturer
When considering drug process changes, the burden resides rightfully with the manufacturer, according to Esua. It is also the manufacturers' responsibility to complete a comprehensive scientific review of the proposed changes, with thorough consideration of all possible implications, and a detailed impact assessment as part of the change control process.

“In the case of the NDMA contamination of valsartan, it is known that dimethylamine could be an impurity in the solvent [drug master file] DMF? Yes. Is it known that dimethylamine would react under the reaction conditions to give NDMA? Yes. Where, then, did the manufacturer go wrong? Were dimethylamine levels higher than anticipated in the DMF (since it’s not a typical impurity that would be screened during a DMF solvent release), or was the combination of these two factors (the presence of dimethyl amine and reactivity in the reaction) simply not considered?” Esua asks.

What is important to remember, according to Esua, is that although a regulatory inspection is a tool to measure compliance against current manufacturing regulations, it does not, nor can it, dictate a certain level of scientific competence on the part of the manufacturers, or unfortunately, the regulatory agencies themselves.

Know your API supplier
So how can drug makers be sure they are selecting API suppliers with the appropriate level of scientific competency? “It is imperative that pharma/biotech companies understand the partners they choose to do business with,” asserts Stephen Houldsworth, director of global small molecules and antibiotics platforms at CordenPharma International. “They must have confidence in the company’s quality systems and its manufacturing team, as well as the team’s scientific competence and ability to make the correct decisions,” he explains.

Houldsworth points out that there are suppliers in the marketplace today that perhaps make decisions based on incorrect assumptions or poor science, the consequences of which are often not discovered until much later, as in the case of valsartan and similar drugs. “Unfortunately, price drives a lot of purchasing decisions—especially in the generic API business—but this cannot be the only priority. Considerations such as quality controls, process development, project management, and scientific expertise must also be factored into these decisions,” he stresses.

The first and most important step is to evaluate and audit the API manufacturer to ensure that it has a sufficient standard of GMP protocols and procedures in place to minimize the risk for cross contamination, according to Jonathan Knight, director of marketing intelligence for Cambrex. The second step is to ensure further evaluation where necessary, such as for potential toxic elemental impurities originating from the environment, the raw materials used for manufacturing, and/or corrosion of manufacturing equipment. “Confirmation is needed that these types of impurities are not present in the API and thus do not impact the product quality,” Knight observes.

In addition, Cambrex suggests reviewing the company’s regulatory history and its corrective actions around observations and GMP compliance and training. Additionally, Knight notes, it is important to assess the company’s experience in developing new chemical entities, and the proficiency and experience of its chemical-development, analytical-development, and quality-assurance departments. That includes checking the investment history of a manufacturer, especially with respect to the acquisition of the most up-to-date analytical equipment.

“Having a good understanding of what the potential risks are can be determined by the development of good design of experiments. In addition, ensuring openness between parties and clear documentation can avoid problems,” Knight adds.

The success of a company’s outsourcing efforts is driven by the quality of their vendor qualification and management systems, according to Houldsworth. “They need to be robust, structured, and detailed to provide a high level of confidence that the API suppliers in question are reliable and competent,” he concludes.

Reasonable responses needed
Esua cautions that regulatory agencies should not respond to the valsartan contamination issue with a simple knee-jerk reaction and demand that all process changes must be approved by regulatory agencies before implementation. “Apart from crippling both the manufacturers (via delays in change approvals) and the regulatory agencies (by drastically increased burden of work), this approach would lead to rising costs in an industry that is already under intense pressure from a costing point of view, without any guarantee that problems will be avoided in the future,” he states.

References
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Efficient delivery of therapeutics is at the core of successful drug therapy. While the delivery of small molecules and systemically acting biologics is now a practiced art, the delivery of biologics into cells (such as the intracellular delivery of a gene therapy) and the application of cells themselves as the therapeutic is an area requiring further optimization.

In the case of cell therapy, such as stem cell-based regenerative medicine approaches, it is known that ~95% of cells either die on administration or migrate away from the site of application, inhibiting efficacy and introducing safety risks. New technologies are therefore required to retain cells at the disease site and for them to remain viable and functional for local tissue repair or regeneration. One such innovation is Locate Bio’s TAOS platform which is an injectable matrix specifically designed for the administration and localization of advanced therapies, such as stem cells (1–3).

For the intracellular delivery of biologics, the challenge is to get a relatively large payload across the cell membrane to the cytoplasm or organelle of action. Gene therapies, even using plasmid DNA (pDNA) of small size 3 kbp, represent ~2000 kDa molecules, which do not readily cross the cell membrane unlike small molecules. While cellular uptake mechanisms exist, they can trap such therapeutics in intracellular vesicles (endosomes), sequestering them away from the site of action (for pDNA transfection this being the nucleus), and rendering them inactive.

**Gene therapy**

Gene therapy approaches can be divided into ex-vivo cell modification and direct in-vivo applications. The former includes the introduction of new functional genes into autologous (patient-derived) cells, which are then given back as therapy, such as CAR-T engineered T-cells (with cancer targeting receptors) or hematopoietic stem cells with replacement or corrected genes to augment patient immunology. The present approaches are largely focused on physical methods such as electroporation (the use of electrical potential to make cell membranes transiently permeable), which are detrimental to viability, or the use of engineered viruses, such as lentivirus, which have evolved to penetrate cells and hijack host cellular machinery to integrate and express genes ectopically. Both routes have been extensively used to deliver genetic cargos such as plasmid DNA, transposon systems or ribonucleoprotein expression such as CRISPR/Cas9 to enable stably retained gene editing. Non-viral systems, including lipid nanoparticles (LNPs), synthetic vectors, and cell penetrating peptides (CPPs), have long promised to overcome the limitations of viral delivery methods and physical methods (such as electroporation), as safe, cost-effective, and versatile alternatives (4). In the case of ex-vivo applications, where permanent effects are required, integrating viruses such as lentivirus and retroviruses are commonly used.
In-vivo gene therapy presents different challenges, as it is much more difficult to apply physical methods such as electroporation to tissues, although ‘gene gun’ approaches (using pulses of pressurized gas) are available for local intramuscular delivery. The mainstay of in-vivo gene therapy approaches is the use of viruses, predominantly AAV or lentivirus, which can transduce many cell types within the body. However, these systems have limited tissue specificity or targeting, require high doses of virus to achieve therapeutic levels of target tissue gene expression, and also present key challenges in terms of safety (the risk of mutagenic integration into the genome and viruses regaining the ability to replicate), tolerability, and cost of goods. Viral delivery systems can only be utilized as gene therapy vectors and are not compatible with the delivery of other biological molecules such as peptides, ribonucleoprotein, or RNA drugs.

Non-viral systems have long promised to overcome the limitations of viral delivery methods and physical methods (such as electroporation), as safe, cost-effective, and versatile alternatives (4). However, to date, they have suffered with their own limitations—principally lower efficacy and higher cell toxicity. Next-generation approaches in development are making large inroads into overcoming these barriers to widespread use as intracellular delivery systems.

Advanced cell penetrating peptides

Cell penetrating peptides (CPPs) have emerged as potential therapeutic agents due to their intrinsic ability to enter cells and mediate uptake of a wide range of cargos by endocytosis (5–7). Historically, however, the use of CPPs has been hampered by inefficient delivery to the intended cellular compartment (e.g., nucleus or cytoplasm). Typically, micromolar concentrations may be required to obtain high levels of transfection, and even where these levels can be achieved (e.g., ex-vivo) it can be toxic to the target cell, resulting in relatively low transfection efficiency overall.

To overcome this inefficiency, an approach using a novel peptide-based intracellular delivery system (IntraStem, Locate Bio) uses the method of glycosaminoglycan (GAG) enhanced transduction (8). This family of non-viral vectors utilizes a peptide that fuses a heparan sulfate GAGs binding domain with a classical CPP to achieve a highly synergistic increase in transfection rates. This can be used as a delivery system to deliver a range of biologic molecules into cells, through a simple complexation process involving electrostatic condensation of the peptide and payload to create nanoparticles, which are readily taken up by target cells. For example, high molecular weight nucleic acids (such as pDNAs) are rapidly condensed to form compact stable nanoparticles (80–100 nm), which provides protection to the payload as well as facilitating diffusion through biofilms and bio-
logical barriers to reach target tissues in-vivo. Importantly, this approach has been shown to deliver a wide range of cargos in-vitro including recombinant fluorescent proteins, transcription factors, antibodies, drug-loaded nanoparticles, and enzymes, with uptake levels up to two orders of magnitude higher than previously reported in cell types considered hard to transduce (8).

Somewhat surprisingly the IntraStem system does not exhibit the expected toxicity profile of classical CPPs—due to less reliance of cationic charge (8)—and it has been shown to preserve cell viability and stem cell potency. In a study comparing various transfection reagents (considered to be in-vitro industry gold standards) and the peptide-based intracellular technology, the latter was found to exhibit low toxicity and maintain post-transfection cell proliferation rates, allowing repeated or sustained administration of the biologic to cells (Figure 1). Through repeated and sustained administration of the IntraStem delivered therapeutic to target cells, it is possible to achieve a high level of payload expression while preserving their viability and potency. This makes the approach particularly attractive for applications where target cells numbers are particularly low, restricted, and/or sensitive to other transfection methods.

Therapeutic applications
The IntraStem system has also been used successfully by various academic groups. These include the generation of induced pluripotent stem cells (iPSCs) using episomal vectors (Figure 2), and in the delivery of gene editing technologies (e.g., CRISPR/Cas9 to iPSCs) ex-vivo to correct genes or generate disease models (9).

To assess the IntraStem technology in-vivo, various tailored formulations have been tested in a number of pre-clinical models, including lung and brain models, with promising results (10). Moreover, there was no evidence of acute toxicity following administration, indicating the non-immunogenic potential of IntraStem particles (10). Furthermore, direct modification of the peptide, the addition of accessory peptides, and/or additives to the transfection complex can further optimize tissue penetration, transfection efficiency, and/or the longevity of expression of the nucleic acid, giving a tunable and versatile intracellular delivery system.

Conclusion
As an attractive alternative to physical or viral methods of transfection, next-generation peptide-based intracellular delivery systems provide an efficient means of delivering a range of therapeutic biomolecules into a wide array of cell types. Locate Bio is currently developing its IntraStem technology for both ex-vivo and in-vivo therapeutic applications following encouraging data generated by a range of academic groups. The evidence to date supports the potential therapeutic application of IntraStem as a delivery system in the treatment of a variety of diseases. These could include gene augmentation or gene editing approaches for cell therapies or direct gene therapy in the body, either through local or systemic delivery (9–11), or non-DNA based treatment approaches.

References
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- Unattended Perimeter Monitoring
- Emerging/Novel Biological Threat Sensing
- Medical Artificial Intelligence
- Autoinjector Development and Drug Manufacture to Deliver MMB4/Atropine
- Single Chamber Autoinjector to Deliver Small Molecule Nerve Agent Therapeutic

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Cleaning Processes

Liquid chromatography is used for separating materials in biopharmaceutical production, primarily for purifying proteins by separating product and impurities. The stationary phase in liquid chromatography uses fine, solid beads referred to as resins that are packed and held in a column by meshes. These particles can be physically or chemically modified to provide specificity to grab or repel molecules within mixtures.

Regenerating resins
Chromatography resins are typically dedicated to a single product. They can be either disposed of or cleaned to an acceptable level to render them suitable for use in subsequent cycles. The decision to reuse or dispose of resins is primarily driven by a cost analysis (1–2). For that reason, biopharmaceutical manufacturers reuse chromatography resins multiple times to make them affordable for inclusion in downstream processes (3–4). Regenerating or “cleaning” the resin is necessary for this purpose. The process consists of removing residual proteins and impurities from the resin while inside the column. Regeneration may be done after every loading cycle or after a few loading cycles.

Once impurities bind irreversibly, accumulating over time and consequently deteriorating the chromatography process performance, the resin needs to be regenerated to restore process performance and to minimize the risk of carryover (5). Caustic solutions at concentrations between 0.1–2 M were reported to be effective at regenerating most types of resins (6–7). Caustic solutions have also been effective at inactivating most viruses, bacteria, yeasts, fungi, and endotoxins and can be easily detected, removed, and disposed of. Other publications show that resins are effectively cleaned and sanitized with acidic solutions such as benzyl alcohol (8). Many times, the regenerating solution is used to store the cleaned resin for a prolonged time when not in use either in the column or in a separate storage vessel (7).

Cleaning resin residue
Regeneration of resin as described above has been well documented. Cleaning of the resin residue itself specifically from process equipment surfaces has not been widely addressed. While the resin packing is typically dedicated to one product, the chromatography column system may be employed for multiple products. After cleaning, the resins may be placed in another vessel for short or long-term storage. Other equipment that may have indirect contact with the resin are the slurry and packing tanks, and smaller parts such as hoses and valves. All these items must also be free from resin residues prior to use on the next product batch.

Most cleaning validation approaches are centered around removing either protein or process impurities from surfaces, and not on the resin residue itself. Residues from a chromatography resin are different from a protein in multiple ways. For example, the resin size may be more than 3000 times larger than a protein. As a general rule, the longer and more complex a molecule is, the harder it is to clean. Also, proteins in general degrade in the presence of caustic so-

Laboratory test methods evaluate cleaning agents and cleaning process design for non-dedicated chromatography columns systems.

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Residues from a chromatography resin are different from a protein in multiple ways.

For removing resin residues, the most commonly used solutions are sodium hydroxide (NaOH) and sodium chloride (NaCl), or even hot water for injection (WFI). Nonetheless, the physical and chemical properties of resins may be quite different from other residues of typical cell-culture processes.

Cleanability studies should be conducted to demonstrate the suitability of these commodities for cleaning non-dedicated chromatography columns and to ensure that there is no cross-contamination between resins used for previously manufactured product into the next product. Cross-contamination concerns may also include microbial or allergen risks. This paper provides a case study that evaluates the cleaning efficacy of NaOH and formulated cleaning agents against resin residues.

A general recommendation for cleaning resin residues is provided.

Defining the design inputs and outputs for cleaning resins is an important part of the cleaning process design. Cleaning parameters for a wash step may include the cleaning agent, concentration, temperature, time, cleaning method, water quality, and environmental factors (9). Cleaning agents should be selected based on laboratory studies that simulate the soil condition and cleaning method used as well as performing a supplier qualification and technical support review. A good experimental design must be used to identify the parameters that have a significant impact on cleaning within a selected range (10–11).

**Laboratory test model**

Manufacturing process parameters, such as dirty hold time, materials of construction, and soil conditions should be well understood before designing the cleaning process. Understanding all these factors will lead to a better design of the laboratory test model. As seen in **Figure 1**, laboratory testing can include coating of the soil onto a stainless coupon and conditioning it in an oven for a specified time and temperature (12). After the coupon is conditioned, it can be cleaned by several different cleaning methods.

In a laboratory set up, agitated immersion may be conducted as a standard for cleanability studies. Agitated immersion consists of the cleaning agent solution mixed in a beaker and equilibrated to temperature and concentration. The coupon is conditioned with the resin soil and placed into a beaker containing the cleaning agent. At select intervals, the coupon is visually inspected and either returned to the cleaning agent for additional time or evaluated for cleanliness using analytical methods, as needed. This cleaning method is generally considered worst-case when compared with clean-in-place systems because minimal action is employed.

The following discussion centers on the cleanability of various resins used and submitted by a biopharmaceutical company located in the United States. The biopharmaceutical site had concerns about the suitability of its current cleaning procedure using a commodity chemical (NaOH) for removing resin residues from the chromatography column and other ancillary equipment.

**Cleanability case study**

**Laboratory evaluation and conditions.** A total of seven different resins were evaluated: Q Sepharose XL Resin (GE Healthcare Life Sciences), SP Sepharose FF Resin (GE Healthcare Life Sciences), Butyl Sepharose HP Resin (GE Healthcare Lifesciences), ProSep vA Ultra Resin (MilliporeSigma), MabSelect SuRe Resin (GE Healthcare LifeSciences), Ceramic Hydroxyapatite Resin (Bio-Rad Laboratories), and.png
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Poros XS Resin (Thermo Fisher Scientific). The detailed test procedure is described in Table I and samples of resin-coated coupons are shown in Figure 2.

The critical parameters investigated during the cleaning process design testing included varying wash times, cleaning chemistries, cleaning agent concentration, and temperature (see Table II). The dirty hold time (air-dried for 48 hours and baked at 121 °C for one hour), cleaning action (low agitation, spray wash, and cascading flow), water quality (de-ionized), and surface characteristics (304 stainless steel with a 2B finish) were unchanged for this study.

A coupon was considered clean if it was visually clean, water break free, and if the difference between its pre-coating weight and post-cleaning weight was not detectable (0.0 mg of residue) (13). Refer to Table II for a sample summary of study details.

A cleaning validation and changeover approach should consider resin removal from process equipment. The type of resin, temperature, and cleaning agent selection had a significant impact on cleanability of the stainless-steel coupons used in the study to evaluate the performance of various cleaning agents in removing residues of common chromatography resin residues from a stainless-steel surface. A potassium hydroxide-based formulated cleaning agent at 1% v/v up to 60 °C for up to 60 minutes was effective in cleaning the residues. Even though NaOH is widely used in the biopharmaceutical industry for cleaning resins, it did not perform as well as the potassium hydroxide-based formulated cleaning agent within this study. For some resins, a phosphoric acid-based cleaner was also effective in cleaning the residue and may be added as a secondary step particularly for mineral-based resins.

**Table I: Laboratory test procedure.**

<table>
<thead>
<tr>
<th>Step</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dried and cleaned 304-grade stainless steel coupons (7.5 x 15 cm size) were weighed on an analytical balance (±0.1 mg) to obtain the pre-coating weight.</td>
</tr>
<tr>
<td>2</td>
<td>Coupons were coated with 3–5 mL of the sample. The amount of residue per surface area was controlled and recorded (see Figure 2).</td>
</tr>
<tr>
<td>3</td>
<td>The coated coupons were air-dried at ambient temperature for 48 hours or baked at 121 °C for one hour.</td>
</tr>
<tr>
<td>4</td>
<td>The coated coupons were weighed on an analytical balance to determine the pre-cleaning weight.</td>
</tr>
<tr>
<td>5</td>
<td>Each coupon was cleaned by agitated immersion, spray wash, or cascading flow.</td>
</tr>
<tr>
<td>6</td>
<td>Each coupon was removed and visually observed for cleanliness.</td>
</tr>
<tr>
<td>7</td>
<td>Each side of the coupon was rinsed with tap water for 10 seconds at a flow rate of 2 L/min.</td>
</tr>
<tr>
<td>8</td>
<td>Each side of coupon was rinsed with deionized water and examined for a water break-free surface.</td>
</tr>
<tr>
<td>9</td>
<td>Coupons were dried and then weighed on an analytical balance to determine the post-cleaning weights.</td>
</tr>
</tbody>
</table>

**Figure 2: Samples of resin coated coupons prior to cleaning.**

Q Sepharose XL Resin  
Butyl Sepharose HP Resin  
SP Sepharose FF Resin  
ProSep VA Ultra Resin

**Conclusion**

A cleaning validation and changeover approach should consider resin removal from process equipment. The type of resin, temperature, and cleaning agent selection had a significant impact on cleanability of the stainless-steel coupons used in the study to evaluate the performance of various cleaning agents in removing residues of common chromatography resin residues from a stainless-steel surface. A potassium hydroxide-based formulated cleaning agent at 1% v/v up to 60 °C for up to 60 minutes was effective in cleaning the residues. Even though NaOH is widely used in the biopharmaceutical industry for cleaning resins, it did not perform as well as the potassium hydroxide-based formulated cleaning agent within this study. For some resins, a phosphoric acid-based cleaner was also effective in cleaning the residue and may be added as a secondary step particularly for mineral-based resins.
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## Cleaning Processes

### Table II: Summary of testing conditions and results for the agitated immersion cleaning method. The coated coupon was immersed in a 1500-mL beaker filled with a cleaning solution, and the solution was agitated at a mild speed using a magnetic stirrer. Formulated H\(_3\)PO\(_4\) is formulated cleaner containing phosphoric acid, and Formulated KOH is formulated cleaner containing potassium hydroxide. Concentration of 0.2 M is equivalent to 2 g/L.

<table>
<thead>
<tr>
<th>Resin (baked on at 121 °C for 1 hour)</th>
<th>Temp (°C)</th>
<th>Conc (% v/v)</th>
<th>Cleaner</th>
<th>Washtime (min)</th>
<th>Visual observation</th>
<th>Water break free (WBF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q Sepharose XL Resin</td>
<td>60</td>
<td>N/A</td>
<td>Deionized water (DI)</td>
<td>60</td>
<td>Moderate</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>0.2 M Sodium hydroxide (NaOH)</td>
<td>Moderate</td>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Formulated H(_3)PO(_4)</td>
<td>Trace</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Formulated KOH</td>
<td>Visually clean</td>
<td>YES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP Sepharose FF Resin</td>
<td>60</td>
<td>N/A</td>
<td>DI</td>
<td>60</td>
<td>Moderate</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>0.2 M NaOH</td>
<td>Moderate</td>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Formulated H(_3)PO(_4)</td>
<td>Trace</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butyl Sepharose HP Resin</td>
<td>60</td>
<td>N/A</td>
<td>DI</td>
<td>60</td>
<td>Moderate</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>1 Formulated KOH</td>
<td>Visually clean</td>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ProSep vA Ultra Resin</td>
<td>60</td>
<td>N/A</td>
<td>DI</td>
<td>60</td>
<td>Moderate</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>1 Formulated KOH</td>
<td>Visually clean</td>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MabSelect SuRe</td>
<td>60</td>
<td>0.2 M NaOH</td>
<td>Visually clean</td>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>Formulated KOH</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceramic HA Resin</td>
<td>60</td>
<td>0.2 M NaOH</td>
<td>Visually clean</td>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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FDA, early adopters, and industry groups continue to promote use of continuous manufacturing (CM) of oral solid-dosage (OSD) drugs as an approach for modernizing pharmaceutical manufacturing.

In a Feb. 26, 2019 statement (1), then-FDA Commissioner Scott Gottlieb, MD, and Janet Woodcock, MD, director of FDA’s Center for Drug Evaluation and Research (CDER), said, “We’re encouraged to see a growing number of companies embracing CM. It’s a key step towards promoting drug quality and improving the efficiency of pharmaceutical manufacturing. We’ve worked hard to help industry develop the tools to start advancing these goals. The FDA is committed to helping more companies advance these CM platforms owing to the public health benefits of these more modern approaches. We support the early adopters that are embracing this innovative technology, and we look forward to working with other interested companies.”

FDA’s support includes the February 2019 release of a draft guidance for industry, *Quality Considerations for Continuous Manufacturing* (2), which outlines some of the regulatory considerations that are unique to continuous manufacturing in an effort to clarify the agency’s current thinking and support CM development. In addition, FDA’s Emerging Technology Team (ETT) is charged with helping “early adopters of CM (and other advanced manufacturing technologies) surface and resolve implementation challenges and navigate the application review process for products made with these modern methods,” Gottlieb and Woodcock noted in the statement.

At the 2019 International Forum for Process Analysis and Control (IFPAC), several of the early-adopter companies shared some of the lessons learned in the past year or two as they have moved forward with CM implementation. In these presentations, the CM technical community expressed dedication to building industry-wide understanding of CM so that it can be used more broadly to improve manufacturing quality.

**Flexible batch sizes**

One of the benefits of CM is the opportunity to better match supply to demand. The concept of batch size, however, is one of the concerns that some companies may have when considering whether to move to CM. This issue is addressed by the FDA draft guidance, and industry members are experimenting with possibilities. The guidance explains that a batch can be defined “based on the production period, quantity of material processed, quantity of material produced, or production variation (e.g., different lots of incoming raw material), and can be flexible in size to meet variable market demands by leveraging the advantage of operating continuously over different periods of time” (2).

At Merck, known as MSD outside the United States and Canada, a CM team is working on converting a batch process to a CM process for a drug product with multiple strengths. The aim is to be able to have short or long-duration runs (i.e., small or large batches) that will make product to meet market demand with less inventory. The Merck team worked with equipment supplier GEA to probe the upper limit for batch sizes by running continuously for 120 hours (five days); the tablet compression and coating process ran successfully with no problems in material build-up or feeder control (3).
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Pegylation is a well-known technology used to increase residence time of L-asparaginase in blood circulation and to reduce hypersensitivity reactions; however, it is important to address manufacturing problems associated with the shorter shelf-life of pegylated L-asparaginase (pegaspargase) upon long-term storage in the form of a solution. Exposure to the sudden excursions encountered during storage and shipping may affect stability of the pegaspargase drug product material. In this article, the effect of freeze-thawing and high temperature on the stability of pegaspargase protein was studied. Differences in the degradation pathways for the storage conditions were identified, and manufacturing issues associated with the degradation are discussed. It was observed that pegaspargase follows different degradation pathways when exposed to freeze-thawing and high temperature stress. These differences in the degradation pathways have different implications on the manufacturing process.

L-asparaginase has been extensively investigated for the treatment of acute lymphoblastic leukemia (ALL) (1). The role of L-asparaginase present in guinea pig serum in the reduction of lymphoma was first studied by Broome, and the inhibitory effect was attributed to depletion of asparagine due to the presence of L-asparaginase in the serum (2). L-asparaginase enzymatically cleaves amino acid L-asparagine into aspartic acid and ammonia. Depletion of L-asparaginase in blood serum results in inhibition of protein-synthesis, DNA-synthesis, and RNA-synthesis, especially in leukemic blasts that are not able to synthesize L-asparagine and thus undergo apoptosis (3). Normal cells, in contrast, are capable of synthesizing L-asparaginase and are less affected by its rapid withdrawal during treatment with the enzyme L-asparaginase (4).

Native L-asparaginase derived from *Escherichia coli* (*E. coli*-asparaginase: Kidrolase, EUSA Pharma; Elspar, Ovation Pharmaceuticals; Crasnitin, Bayer; Leunase, Sanofi-Aventis; Asparaginase medac, Kyowa Hakko) has been used in the treatment of ALL (5). Although L-asparaginase is an effective antineoplastic agent used in chemotherapy of ALL, development of antibodies against L-asparaginase and hypersensitivity reactions may lead to discontinuation of the treatment (6). Such adverse events along with the other toxicities like thrombosis, pancreatitis, hyperglycemia, and hepatotoxicity led to the development of alternative sources of L-asparaginase (7). The development of L-asparaginase from *Erwinia chrysanthemi* (Erwinase, EUSA Pharma) is an outcome of such efforts (8). The disadvantage of frequent intramuscular injections and the adverse events of hypersensitivity reactions led to development of a pegylated version of native *E. coli*-asparaginase (polyethylene glycol [PEG]-asparaginase: Oncaspar, Enzon Pharmaceuticals Inc) (9). Oncaspar is an asparagine-specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for treatment of patients with first line ALL and hypersensitivity to asparaginase. Oncaspar is available as a solution in a single-use glass vial with the strength of 3750 IU per 5 mL of solution. The recommended dose of Oncaspar is 2500 IU/m² intramuscularly or intravenously. Oncaspar is not recommended to be used when it is frozen or stored at room temperature 15–25 °C (59–77 °F) for more than 48 hours.
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L-asparaginase is a homotetrameric enzyme comprised of four identical subunits with a mass of 34,592 Da coupled by weak, non-covalent, largely hydrophobic interactions (10). The tetrameric structure of the L-asparaginase enzyme is required for enzymatic activity (11). Pegaspargase (pegylated L-asparaginase) is a covalent conjugate of E. coli-derived L-asparaginase with monomethoxypolyethylene glycol (mPEG) succinimidyl succinate (PEG-SS; molecular weight of 5000 Da). Approximately 69 to 82 molecules of mPEG are linked to L-asparaginase. The succinyl linker between PEG and L-asparaginase contains an ester linkage that can lead to hydrolytic removal of the PEG moieties from the PEG-protein conjugate (12). The release of PEG from the protein molecule (i.e., depegylation) upon storage in the form of solution leads to a shorter shelf-life. Also, stability of the protein molecule can be affected by chemical as well as physical factors (13). Proteins can be denatured readily by stresses encountered in solution, or in a frozen or dried state (14). It is also important to know the effect of sudden excursions encountered during shipping of the drug product material, which may affect stability of the product. Drug product may be exposed to lower or higher temperature from its real-time storage conditions during shipment. It is known that L-asparaginase shows changes in its structural and biological properties upon repeated freeze-thaw. In this article, the effect of freeze-thaw stress and high temperature on the stability of pegaspargase (pegylated E. coli-derived L-asparaginase) has been investigated; manufacturing issues associated with these degradation pathways are discussed.

Materials and methods
Preparation of pegaspargase. L-asparaginase was procured in the form of lyophilized powder. PEG of 5000 Da size was procured in the activated form. Pegaspargase was prepared by conjugating (pegylation) multiple units of 5 kDa activated PEG (m-PEG-N-hydroxysuccinimidyl ester) at different sites of the α-NH₂ group of N-terminal residue and ε-NH₂ group of Lysine residues of the L-asparaginase enzyme using the pegylation techniques known in the art (15, 16). Pegylation occurs in all four subunits at the specified sites of the enzyme. The pegylated L-asparaginase (crude solution) was purified to remove excess free PEG using column chromatography (AKTA system, GE Healthcare). Buffer exchange of the purified pegylated L-asparaginase protein solution was performed in the desired formulation media (with final concentration of 5.58 mg of dibasic sodium phosphate, 1.20 mg of monobasic sodium phosphate, and 8.50 mg of sodium chloride in 1 mL of water for injection) by membrane ultrafiltration and diafiltration steps. Ultrafiltration and diafiltration were performed in a controlled manner at room temperature with 50 kDa molecular weight cut off membrane by using a tangential flow filtration system (Sartorius Stedim Biotech). At the end of buffer exchange, the protein solution was concentrated through an ultrafiltration step, and the final concentration was adjusted to approximately 8.8 mg/mL. The protein solution was finally filtered through a 0.2 μm sterile filter (Sartopore 2, Sartorius Stedim Biotech). The final formulation composition was maintained to be the same as that of the commercial product Oncaspar. All the excipients for the final formulation (i.e., dibasic sodium phosphate, monobasic sodium phosphate, and sodium chloride) were obtained from Merck, Germany.

Freeze-thawing and exposure to high temperature. In order to check the effect of freezing and thawing, pegaspargase solution was aliquoted with 500 μL solution in cryo-vials of 1-mL capacity (Nunc CryoTube vials, Thermo Scientific). Samples were frozen at or below –20 °C in a deep freezer (Thermo Electron Corporation, Model No.: ULTI1740-3-V40). Thawing was performed at room-temperature rapidly until the frozen mass was converted into the liquid solution. In order to check the effect of high temperature (forced degradation due to heat), formulated pegaspargase protein solution was filled in 2-mL glass vials (borosilicate USP Type I clear flint glass, Schott) with coated stoppers (fluorinated polymer-coated butyl rubber stopper, West Pharmaceuticals) and sealed with flip-off seals (aluminium seals with flip-off plastic cap, West Pharmaceuticals). Samples were exposed to a controlled high temperature of 40 °C ± 5 °C with 75% ± 5% relative humidity (RH) and 25 °C ± 5 °C, with 60% ± 5% RH in the stability chamber (Thermo). Samples were withdrawn at different time intervals and stored between +2 °C and +8 °C before analysis.

Analytical evaluations. Samples were analyzed by high-performance size exclusion chromatography (HP-SEC) using two different detectors: an ultraviolet (UV) detector and a refractive index (RI) detector. The RI detector was used to detect an increase in free PEG due to exposure of pegaspargase to freeze-thawing and high temperature, if any. Polypeptide profile of pegaspargase protein was also evaluated by analyzing samples using sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE).

HP-SEC of pegaspargase was performed on a high-performance liquid chromatography system (LC 2010–CHT series, Shimadzu) equipped with a YMC Pack Diol-300 column (8.0 × 300 mm; 5 μm). Before injecting the sample, the column was pre-equilibrated with buffer containing 90% 50 mM sodium phosphate (pH 6.8) with 300 mM sodium chloride and 10% 2-propanol at a flow rate of 0.5 mL/min under an oven temperature of 25 °C. After equilibrating the column, 10 μg of sample was injected and analyzed in isotropic mode at a flow rate of 0.5 mL/min, and chromatographic separation was monitored at 214 nm with UV detection or using the RI detector to monitor free PEG in the samples. The polypeptide profile of pegaspargase was obtained under non-reducing conditions. SDS-PAGE was carried out essentially in accordance with the Laemmli method (1970) (17). For non-reducing SDS-PAGE, 4–20% gradient polyacrylamide gel (Bio-Rad) was used. A total of 10 μg of pegaspargase protein was loaded for different test samples on the gel. After electrophoresis, protein bands were developed by either Coomassie R250 (Merck) staining or barium iodide staining using bar-
Sometimes, even if your job focuses on data, you have to look beyond it. That’s why Sanjay and his team at Thermo Fisher Scientific don’t just apply data to solve formulation challenges. They look beyond the data for other potential roadblocks. In the early phase trials of a complex API molecule, his team recognized that dagger shaped crystals were inhibiting flow during production. While short-term workarounds for trials were at hand, they knew that in future scale ups, this would become a significant problem. So they collaborated with teams who modified the API process in advance. Smoothed the crystal. And solved the problem before it became one.

Sanjay Konagurthu, Ph.D.
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ium chloride (Merck) and iodine (Merck). Coomassie R250 is known to be more sensitive compared to Coomassie G250 and is commonly used to stain the protein molecules during SDS-PAGE. Barium iodide forms a complex with PEG and is a well-known technique to stain PEG after gel electrophoresis. In the present work, degradation of pegylated L-asparaginase molecule (aggregation or fragmentation) upon exposure to freezing and thawing or high temperature was detected using Coomassie R250 staining, while the presence of free PEG was detected by barium iodide staining.

**Results**

The effects of freeze-thaw and high temperature on pegaspargase protein were investigated, and differences in the degradation pathways were evaluated.

**Effect of freeze-thaw on stability of pegaspargase.** Pegaspargase protein formulated at about 8.8 mg/mL concentration in 49-mM sodium phosphate buffer in presence of 146-mM sodium chloride was exposed to freeze-thaw stress as described in the previous section (Materials and methods). After thawing, samples were analyzed by HP-SEC and SDS-PAGE. 

Chromatographic profiles obtained with the samples of pegaspargase before and after exposure to the freezing and thawing stress are shown in Figure 1. The chromatographic profile shows that the peak corresponding to pegaspargase appears as a single sharp peak when not exposed to freezing and thawing stress; however, upon exposure to freeze-thawing, the peak appears as a split peak with an increase in a shoulder peak and a decrease in the principal peak corresponding to the pegaspargase. Results obtained with SDS-PAGE analysis of the pegaspargase samples before and after exposure to the freezing and thawing stress are shown in Figure 2. Qualitative analysis of pegaspargase samples by SDS-PAGE under non-reducing conditions shows no significant change in the polypeptide profile of the pegaspargase upon exposure to freezing and thawing stress; however, upon exposure to freeze-thawing, the peak appears as a split peak with an increase in a shoulder peak and a decrease in the principal peak corresponding to the pegaspargase. Results obtained with SDS-PAGE analysis of the pegaspargase samples before and after exposure to the freezing and thawing stress are shown in Figure 3. The chromatogram shows no increase in the level of free PEG in the pegaspargase samples exposed to freeze-thaw stress.

**Effect of high temperature on stability of pegaspargase.** Pegaspargase formulated at about 8.8 mg/mL concentration in 49-mM sodium phosphate buffer in presence of 146-mM sodium chloride was exposed to 50°C for 2.5 hours and analyzed by HP-SEC followed by RI detection to check for increase in free PEG if any.
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sodium chloride was exposed to high temperature conditions (40 °C ± 5 °C; 75% ± 5% RH) for a maximum up to one month as described in the previous section (Materials and methods). Samples were withdrawn at different time intervals and analyzed by HP-SEC and SDS-PAGE.

Chromatographic profiles obtained with samples of pegaspargase withdrawn at different time intervals are shown in Figure 4. It is observed that the retention time and shape of the peak corresponding to pegaspargase changes with time of exposure at high temperature. The peak corresponding to pegaspargase shifts toward higher retention time with increase in exposure time at high temperature conditions. The deformation of the peak corresponding to pegaspargase also increases with time when exposed to high temperature. Results obtained with SDS-PAGE analysis of the pegaspargase samples withdrawn at different time intervals after exposure to high temperature over the period of one month are shown in Figure 5. Qualitative analysis of pegaspargase samples by SDS-PAGE under non-reducing conditions show an increase in low molecular-weight species and the presence of free PEG as analyzed by two different staining methods using Coomassie R250 dye and barium iodide, respectively.

In separate set of experiments, pegaspargase samples were exposed to high temperature conditions (i.e., 40 °C ± 5 °C; 75% ± 5% RH and 25 °C ± 5 °C; 60% ± 5% RH) for up to 15 days and 30 days, respectively. Samples were withdrawn at different time intervals after exposure to high temperature and analyzed by HP-SEC and SDS-PAGE. Chromatographic profiles obtained with samples of pegaspargase exposed to high temperature conditions and withdrawn at different time intervals are shown in Figure 6. It is observed that the level of...
free PEG increases with increase in exposure time under high-temperature conditions.

**Discussion**

When exposed to higher temperature, pegaspargase shows changes in the retention time and shape of the peak corresponding to the pegaspargase protein as analyzed by HP-SEC. The deformation of the principal peak corresponding to the pegaspargase protein indicates a loss of structural integrity, and the shift toward the higher retention time suggests fragmentation of the protein molecule over the period of time upon exposure to the high-temperature conditions. The results obtained with SDS-PAGE analysis also show generation of low molecular weight species or fragmentation upon exposure to high-temperature conditions and corroborate the observations made through analysis of samples by HP-SEC.

Similarly, the significant increase in the shoulder peak and decrease in the peak corresponding to the pegaspargase protein when exposed to freeze-thaw stress. The SDS-PAGE analysis of pegaspargase protein exposed to freeze-thaw stress does not indicate any fragmentation or generation of low molecular weight species upon exposure to freeze-thaw stress.

The increase in the peak corresponding to the free PEG in the chromatograms obtained through analysis of the pegaspargase samples using HP-SEC followed by RI detection indicates removal of PEG from the protein backbone as a function of time when stored at high temperature conditions. When exposed to freeze-thaw stress, pegaspargase shows no increase in the peak corresponding to free PEG indicating no dissociation of the PEG from the protein backbone due to freezing and thawing. These results indicate that pegaspargase degrades through depegylation along with loss of structural integrity when exposed to high temperature; however, under freezing and thawing stress it does not show any depegylation. Under freezing and thawing conditions, the changes in the peak profile for the peak corresponding to pegaspargase were observed to be different than the changes observed when pegaspargase was exposed to high temperature stress, which indicates different effects on the structural properties of pegaspargase under each stress condition.

Oncaspar (PEG-asparaginase, Enzon Pharmaceuticals) in the form of liquid solution is known to have a short shelf-life (eight months) due to removal of PEG from the protein backbone. Also, the storage condition for pegaspargase drug substance is between +2 °C and +8 °C, unlike the majority of biological products that are generally stored in frozen form and are known to...
have longer shelf-lives of approximately two years. These storage limitations necessitate continuous or immediate conversion of drug substance material to the drug product material. Storage of drug substance material longer than the stipulated time frame between +2 °C and +8 °C reduces the shelf-life available to the final drug product as it is susceptible to depegylation. Unlike other biological products, it is not possible to store the pegaspargase drug substance material under frozen conditions without presence of any cryoprotectant, as freezing and thawing may lead to structural changes in the protein of interest and impact the biological activity or storage stability before it is converted to drug product. Operations such as shipment to distribution centers and pharmacies after manufacturing the drug product also take considerable time before the product gets delivered to the doctors for the treatment. Therefore, it becomes important to have maximum shelf-life available to the drug product material.

To bring flexibility in the production of the drug product, it is important to manufacture a drug substance that can be stored for a longer period of time so that the drug product can be manufactured based on the market demand and supply chain efficiency. Also, sudden excursions during shipping of the drug product material may affect the stability of the pegylated L-asparaginase protein. Product may be exposed to lower or higher temperature from the real-time storage conditions during shipment. These can lead to degradation of the pegylated L-asparaginase before it gets delivered to the patient and can show sub-optimal effect during treatment.

**Conclusion**

It is known that pegylation of L-asparaginase increases the retention time of L-asparaginase in blood circulation and thereby increases the half-life. However, exposure of pegaspargase protein to both freeze-thaw and high-temperature stress indicated loss of protein integrity, probably due to significant alteration in the structural properties of the protein molecule. The freeze-thaw stress does not lead to any significant removal of PEG from the protein backbone; however, exposure to high temperature leads to depegylation. These observations indicate that the pegaspargase (pegylated L-asparaginase) follows different degradation pathways under different stressed conditions. Further, stabilization of pegaspargase in solution is required to avoid degradation of the molecule during manufacturing process, upon storage, and shipping. Stabilization against freeze-thaw can also help to decouple the manufacturing process of the drug product from that of the drug substance and can bring flexibility for manufacturing of drug product in a multi-product manufacturing facility.

**Acknowledgement**

The authors are thankful to Dr. Sanjeev Kumar Mendi-ratta, president, and Mr. Chandresh Bhatt, research associate, both in the department of Biotechnology at the Zydus Research Centre, Cadila Healthcare, Ahmedabad, for their scientific guidance and technical support.

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Crucial for pharma development

PharmTech: How important is particle characterization in pharmaceutical development?

Clayton (Freeman Technology): Particle characterization is crucial for the pharma industry because of well-established relationships between parameters such as particle size and shape and characteristics that define clinical efficacy—for example, the dissolution profile of a solid dosage form. However, it’s important to understand how physical properties affect powder behavior in general, and the importance of bulk powder characterization as an equally vital and complementary tool.

Bulk powder properties such as flowability, compressibility, bulk density, and permeability often define or impact aspects of pharmaceutical product performance and processing behavior. For instance, flow properties influence the time taken to blend APIs and excipients to homogeneity, and the ease and uniformity of die filling, which in a tableting process can directly impact the quality of the finished product.

Where bulk powder properties are influential, measurement is essential as they cannot be predicted from a knowledge of particle properties. In fact, powders are actually three-phase assemblies consisting of solid particles, gas, and a certain level of liquid, typically water. Behavior is governed by the interactions between the three phases. Measuring a combination of particle and bulk powder properties is usually the best approach to supporting and optimizing pharmaceutical development and manufacture.

More efficient manufacturing

PharmTech: How can particle and bulk powder characterization help enhance manufacturing efficiencies?

Clayton (Freeman Technology): Particle characterization can help drug developers to detect process relevant problems, such as attrition or contamination, but characterizing bulk powder properties is arguably more informative when it comes to enhancing manufacturing efficiency as it can quantify a range of behavioral properties that directly influence in-process performance. These include powder flow properties under process-relevant conditions, the response of the powder to fluidization and consolidation, and the impact of issues such as moisture uptake or caking.

Wet granulation provides a good illustration of how such data can be used to enhance manufacturing efficiency. Tableting blends are often subject to wet granulation to produce a homogeneous, relatively free-flowing feed that compacts well in the press. However, it can be dif-
ficult to define an effective specification for the granules—a process endpoint—as they are an intermediate rather than a finished product.

Research has shown that the flow properties of granules correlate directly with tablet quality, specifically hardness, which is a typical critical quality attribute (1). It is therefore possible to control a wet granulation process to a successful outcome, through the manipulation of processing parameters, on the basis of a flowability specification. Granules meeting this specification will go on to produce tablets of the required quality. This approach is far more efficient and responsive than working up batches of granules into tablets to determine their quality and significantly more relevant than inferring flowability from particle size measurements, which in isolation, may not reliably differentiate poorly performing materials.

Similarly, studies have shown that bulk powder properties can reliably inform on performance in a range of unit operations including vial filling, blending, die/capsule filling, and compaction (2–4).

Technologies: Present and future

PharmTech: What technologies are currently available for bulk powder characterization?

Clayton (Freeman Technology): United States Pharmacopeia (USP) <1174> lists a number of methods for powder flow testing including angle of repose, flow through an orifice, Compressibility Index and Hausner Ratio (both of which are based on measurements of tapped density), and shear cell methods (5). With the exception of shear cell, these largely manual, traditional methods tend to suffer from poor repeatability and reproducibility, and they provide relatively limited insight into process and product performance.

Dynamic powder testing is a more innovative technique developed specifically to meet growing industrial demands for a comprehensive understanding of bulk powder behavior. Performed using a powder rheometer, dynamic testing quantifies the energy associated with moving a powder under different stress and flow regimes. Powders can be analyzed in a consolidated, moderately stressed, aerated, or fluidized state to simulate the condition in the process of interest. Data are highly repeatable and reproducible, and the technique is sensitive making it particularly valuable for process and product-related studies.

“Research has shown that the flow properties of granules correlate directly with tablet quality, specifically hardness, which is a typical critical quality attribute.”

—Jamie Clayton

PharmTech: Are there any promising technologies in the pipeline that you believe will create a paradigm shift in the characterization of particles and powders in pharma?

Clayton (Freeman Technology): The example of dry powder inhalers (DPIs) is useful in illustrating how developers need to be aware of the properties that impact both product performance and manufacturing efficiency for any given dosage form. Dosator technology is used routinely to produce packaged, uniform, low doses for DPIs. Filling of a dosator tube requires a relatively free-flowing powder but with a certain level of cohesion so that compression forms a secure plug that remains in the tube and transfers securely to the packaging.

In a study investigating the relationship between dosator performance and bulk flow properties, aeration behavior was found to be important (a measure of cohesion), but so too was the impact of inter-
particular friction and mechanical interlocking, which heavily influence the ability of a powder to flow under gravity (6). Such studies highlight the conflicting demands of the production process relative to those for optimal dose delivery. As drug delivery requirements are likely to be a priority, insights into processing performance provide valuable guidance on specifying equipment and optimizing process conditions.

“Dynamic flow properties impact blending performance and die filling, with more free-flowing formulations associated with more uniform dispersion and efficient filling.” —Jamie Clayton

In terms of tableting, experience suggests that dynamic flow properties, compressibility, and permeability are all important characteristics for tablet blends. Dynamic flow properties impact blending performance and die filling, with more free-flowing formulations associated with more uniform dispersion and efficient filling. Permeability influences hopper discharge behavior as well as the release of air from the die during filling. Compressibility is critical in determining response to compaction in the press. The effect of flow additives and lubricants can be assessed through dynamic testing—to determine the impact on flow properties—with shear methods additionally useful for evaluating likely interactions with processing equipment, including the tablet press, and hopper performance.

Characterization challenges

PharmTech: What are the main challenges that developers experience with particle and bulk powder characterization currently?

Clayton (Freeman Technology): From the perspective of powder testing, there are a number of challenges worth highlighting. Firstly, the methods in USP <1174> (5)—with the possible exception of shear cell methods—are not necessarily well-suited to the current requirements of the pharmaceutical industry. These techniques offer simplicity but provide minimal information on which to base product or process development.

Shear cell methods are useful for hopper design and more broadly for investigating a powder’s ability to transition from a static state under moderate to high stress. While modern shear testers now deliver good reproducibility, the technique is not always suitable for understanding the performance of powders in the low stress/aerated state that prevails in many pharmaceutical operations. Shear cell testing is also perceived by many as a relatively complex, expert task, and outsourcing remains commonplace.

Dynamic testing provides the most insightful data for product and process optimization, and the instrumentation used typically also allows shear and bulk powder property measurement, delivering comprehensive, multi-faceted powder characterization that supports an optimal approach in product development and powder processing. The challenge is of course justifying the initial investment associated with such instrumentation, though experience demonstrates that the payback is highly beneficial.

PharmTech: Are efforts being made to address these challenges?

Clayton (Freeman Technology): A recent advance that directly addresses issues associated with shear cell testing is the commercialization of uniaxial testing. Uniaxial testing ranks powder flowability via the same metric as shear cell testing but employs a simpler, more direct technique. Testing is fast, intuitive, and highly repeatable/reproducible, and equipment costs are low. Uniaxial testing can therefore offer a good solution for those needing a simple, modern, easy-to-use technique that delivers robust, high quality data.

With respect to investing in more powerful powder characterization technology, the tangible benefits of having access to better data have become much clearer over recent years. It is now far easier to understand how powder testing will support development, manufacturing, and troubleshooting with recent insights from industry leaders highlighting the potential for economic gain.

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Successful technology transfer depends on the ability to anticipate risks and plan ahead.

Successful technology transfer is essential to enable biopharmaceutical clients to safeguard supply, improve distribution, and reduce program costs and risks. When a customer approaches a contract development and manufacturing organization (CDMO) to gain technology transfer support, it is important to confirm that the CDMO has a proven history and a robust project management and technical platform in place. This helps ensure the ability to understand and execute against the project requirements, mitigate risks, deliver the project on time, and right first time. There are several key tools and best practices that enable the team to plan and deliver successful results, including mechanisms to overcome obstacles that may arise.

Table I provides a list of questions for a pharma company to ask a potential CDMO partner.

People and communication are key to project success
To ensure that the technology transfer is successful, the project leader will establish a cross-functional team comprising subject matter experts (SME) for each function. These functions should be matched at customer and CDMO locations where possible. It is important the team establishes a strong partnership and lines of communication such that key roles can work closely with their counterparts throughout the project.

Establishing a communication plan and understanding each other’s escalation channels is crucial at the project start. Early in the project, reaching a level of trust and transparency can take time. To help, both companies must share all relevant details available, including product requirements, history, drivers, and any other information that will help understand one another’s needs. Project kick-off is best handled face to face as the team starts their relationship. It is important to have frequent face-to-face working sessions to allow the team to accomplish deliverables, especially if a significant obstacle arises.

As part of the communication plan, the teams must align on tools to manage the project and operate from a single ‘source of truth.’ This helps ensure alignment on expectations, timing of key deliverables, and communication between the organizations.

Project kick-off, and the conversations leading up to this point, represents a critical period where information sharing begins, and the project could suffer a delay if key information is missed at the start. A pre-defined checklist can assist the team in collecting all relevant information, as well as drive harmonization, incorporate lessons learned from previous projects, and proactively collect key data.

As timelines are often compressed, it may be tempting to jump into project activities immediately. Experience shows, however, that taking time to understand both companies’ requirements pays dividends, ensuring that important factors are not overlooked. For example, there may be differences in procedures for ordering equipment or materials, or shipping and receiving materials; change control processes; and document approval processes. As the project progresses, alignment will also be needed on validation strategy, and testing and inspection requirements. If this alignment does not occur early in the project, the timeline can be negatively impacted.

At the outset, the two teams should agree on a governance model, such as a steering team, which may be one tier of seniority above the project team. This
Successful Technology Transfer

Pharmaceutical Technology spoke with Roger Croucher, senior manager, R&D projects, at Catalent Pharma Solutions; Daniel M. Bowles, senior director, chemical development, at Cambrex; and Kurt J Kiewel, director, new product development and analytical services, also at Cambrex about best practices for a successful technology transfer.

Preparing for a tech transfer
PharmTech: What are the first steps that should be taken when starting the process of tech transfer?

Bowles and Kiewel (Cambrex): The early transfer of information between companies is critical to a successful process transfer. At the RFP [request for proposal] stage, the receiving site should review the information provided and set up a teleconference to fully define the goals of the transfer and discuss the information provided in detail. The discussion between the technical staff on both sides helps to fill in any gaps in the information and to eliminate any ambiguities in the RFP and assumptions in the proposal. Early alignment between parties allows a proposal to be tailored to the precise goals of the program and reduces unnecessary back-and-forth during the proposal generation process. When possible, representatives from the receiving site should travel to the sending site in order to witness key operations first hand.

Croucher (Catalent): The first step in allowing for a successful tech transfer is to evaluate the overall organizational impact in terms of operations, analytical, and quality. Then, the customer should provide a robust technical transfer information packet to the contract development and manufacturing organization (CDMO) to ensure all pertinent information is shared. Where a robust information packet is not available, a risk management approach and governance reviews become even more important. This information packet will include GMP [good manufacturing practice] batch records, special processing items (i.e., there are important processing steps that can be gained by talking to the actual operators, scientists, and engineers that played a role in the initial work performed, then these items are critical pieces of information that can make the difference in having a successful tech transfer), development reports (ranging from small lab-scale, and specific methods; such as in process moisture, exipient release, and finished process testing. Equipment variability is also important (like-for-like equipment may or may not be available); working with a CDMO that has the experience in accounting for such variability, ensuring that the right size of equipment is available, and that the operating procedures for the specific project are confirmed as suitable and/or revised is a key element to a successful tech transfer.

PharmTech: Should both entities be involved in developing the tech transfer process?

Croucher (Catalent): Yes. Subject matter experts (SMEs) from the transferring site and the recipient site should be a part of the handover teams. In my experience, most successful transfers involve an intermediary from the transferring site to ensure the successful transfer of documentation, etc. The technical team from the customer’s company have the knowledge of the product and processes involved, while the CDMO’s technical team understands the available site infrastructure capacity, technologies, and equipment. Marrying these two groups, and their areas of expertise, is critical to a smooth transfer and a shared understanding of the product.

Sponsor companies will often have to consider many factors before they decide whether to produce a product in-house or to outsource. This decision may include factors such as how their global assets are being utilized, how efficiently they can produce now and in the future, and whether their own manufacturing network or that of an external contract manufacturing organization (CMO) or CDMO offers the better scalability to meet the sponsor’s aspirations for the product. The period before work commences, sometimes referred to as the planning horizon, therefore may be much greater for internal transfers than it is for the CMO or CDMO and can even be considered strategically by the sponsor company. If the decision is to use an external vendor, then an assessment or selection process is required to choose the correct partner, and that will often include an evaluation of what efficiencies or other benefits can be expected by outsourcing. This, in turn, requires some degree of disclosure to potential partners, and careful assessment by the sponsor company. Commercial terms need to be reached and, of course, an agreement to be made on how the tech transfer process teams will work together, including detailed comparisons of how policies and procedures compare. This naturally takes time and careful planning and may lead to the program starting later than it may have for an internal transfer.

Bowles and Kiewel (Cambrex): The receiving site should drive the transfer process, as it will ultimately be responsible for adherence to internal SOPs [standard operating procedures] and the final outcome of the transfer. The manner of transferring a specific technology or process from site to site should not be developed in an ad-hoc manner, but instead by following a clear, well-defined, SOP-driven method, regardless of whether the transfer is within a company or between a sponsor and CDMO.

Inter-company transfers should start at the early development stage with an understanding that the process is being developed for transfer to a known inter-company site, and unit operations should be developed with the full knowledge of both sites’ capabilities. Additionally, analytical methods should be developed for instrumentation which has been harmonized between sites in order to streamline method transfer.

Best practices and challenges
PharmTech: What are some best practices and challenges in technology transfer, and how are these addressed? Are there specific considerations when it comes to large-molecule products/processes versus small-molecule?

Bowles and Kiewel (Cambrex): One of the key challenges facing technology transfer for manufacturing is the difference between equipment and specific reactors at different facilities. For internal transfers within a company, standard practice should be that the development work done at the developing/sending site is carried out with careful consideration for the equipment capabilities of the receiving site—a true one-company approach.

Croucher (Catalent): Time-to-market constraints can be challenging, as can insufficient documentation of processes, and key equipment capabilities. The main way to overcome these challenges and ensure a successful tech transfer is by establishing open communication streams between the sponsor and the CDMO, along with regular project reviews and updates. Having strong project management and technical teams will help move the project along to completion efficiently too, because the collective wisdom and experience of the team can overcome most problems given enough notice. While timelines are a key driver to product development, small investments in process improvement or early formulation development to improve product performance can lead to substantial savings later, as well as reveal opportunities for improved market positioning. Given the number of products a CDMO works on every year, innovators should expect their CDMOs to provide thoughtful input into development throughout the life of the product.

The key to any successful tech transfer is the understanding that each molecule is unique and will have its own set of challenges. How a CDMO prepares for any foreseen and/or unforeseen challenges can determine the molecule’s success. Utilizing a risk management approach throughout each stage of the project will assist in airing, addressing, and overcoming challenges as the program moves through each phase of its introduction and throughout life.

―Susan Haigney
team will monitor key project milestones and risks that may arise and take action on items escalated as requiring a decision. Additionally, a global technical forum can help connect global SMEs and functional leaders with the project teams quickly should technical issues arise. This model provides access to global resources and diverse perspectives, offering an additional level of technical oversight, decision making authority, and ability to mobilize resources as required to advance the project. The model also enables trends to be understood and learnings to be shared across the network.

The use of team huddles and visual boards is another tool to help drive understanding, accountability, and efficient decision making as the team executes the project. Visual boards are beneficial to represent the process, assign resources and action items, and flag issues. Huddles are key to efficiently aligning the team and functional management on project-related matters, as well as to recognizing the team’s accomplishments.

Proactive risk management and a ‘right-first-time’ mentality

The ultimate goal of technology transfer is to deliver the new medicine, at the highest quality, to the patients who need it, when they need it; therefore, the final process must be repeatable and well controlled. To minimize delays, the team must have a relentless focus on ‘right-first-time’ execution. Robust procedures, quality controls, and personnel training must be in place to enable the team to bring in each deliverable within the highest quality standards. A right-first-time mentality is essential as part of the team’s culture. This begins with risk management to track, identify, and mitigate any potential risks, with a focus on ‘what could go wrong’?

Several risk management tools are available for technology transfer, such as formal assessments typically performed on the safety, quality, and overall process; others are part of the lifecycle validation process to identify, understand, and control the process. One major component of a successful risk management program is the use of a ‘risk register’ tool to document and track potential risks, requiring an action plan for each risk identified.

A comprehensive launch readiness tool has proven key in identifying potential risks. A risk management tool may include as many as 200 questions across the ‘seven Ms’ of machines, materials, manpower, manufacturability, market, measurement, and mitigation (Figure 1). These questions examine what could go wrong and incorporate lessons learned from previous projects across the network. The tool is updated regularly throughout the project to help track any new risks that arise or are resolved. Each potential risk identified requires development of a mitigation plan with clear actions, timing, and owners. This tool is useful in keeping stakeholders and executive leadership updated throughout the project.

Stage-gate meetings (also known as milestone reviews) are necessary for the team to review relevant data, accomplishments, and risks. Typically, these meetings include steering team or company leadership representation, depending on expectations set at the project start. The stage-gate will determine whether the team is ready to proceed to the next phase of the project, or whether additional development work or process improvements are required.

As transferring a new process to the facility typically demands new equipment/technology, materials, and other requirements, the team should con-
sider which aspects need particular attention. These may include a combination of additional hands-on training, clarity to batch record and procedure instructions, pre-execution readiness huddles, and additional on-the-floor technical support. It is important to share observations and learnings and ask for feedback from users of the new processes to ensure new requirements are well controlled. These controls must be incorporated into the final process.

The technology transfer network should continuously evaluate the project management toolkit, helping optimize and enable successful technology transfers.

Upon successful completion of the project, a final stage-gate meeting should be held to capture learnings and improvements prior to production turnover, including a ‘lessons learned’ meeting with participation from both companies. Learnings should be shared across the site and network and incorporated into future projects.

The technology transfer network should continuously evaluate the project management toolkit, helping optimize and enable successful technology transfers. This evaluation can be facilitated through a monthly forum and face-to-face workshops with the global technology transfer team. The team can pilot new initiatives and tools at their site before finalizing and standardizing across the network. Similarly, this global forum is key to leverage knowledge and resources to manage the overall project portfolio.

Quality by design as an aid to technology transfer

In addition to a robust project management toolkit, for a technology transfer to be successful, the principles of quality by design (QbD) should be used to ensure a robust understanding of the process and design principles.

For large production batches to run smoothly, drug formulators need to be mindful of a compound’s performance, stability, and manufacturability from the earliest stages, and throughout formulation and process development. While drug product development scientists typically work on formulation development and stability improvement in Phases I and II of clinical trials, manufacturability is not always a priority. Scale-up, however, may not be straightforward or predictable if process knowledge that is scale-independent has not been developed. This knowledge should guide equipment selection, link the critical process parameters (CPPs) to critical quality attributes (CQAs), and establish the design space (DS). Sound scientific/engineering principles and mechanistic models should be employed whenever possible for scale-up of pharmaceutical unit operations. In addition, a robust risk assessment program invoking QbD principles at each stage of development is crucial for successful scale-up and transfer.

Process scale-up of pharmaceutical unit operations and understanding through models should be developed whenever possible. Models that describe pharmaceutical unit operations can generally be based on empirical, semi-empirical, and mechanistic approaches.

Predictive modeling

Models describing formulations and unit operations should be developed early in the process to avoid a trial-and-error approach. Formulation models are critical to understand the interplay between drug and excipients and provide a fundamental basis for rational formulation design in line with QbD principles. Figure 2 is a molecular dynamics model showing the effect of drug loading on a spray dry dispersion.

Mechanistic models for understanding the thermodynamics of unit operations (e.g., spray drying) are essential to predict the operating ranges a priori to running the actual process. Thermodynamic modeling of the process allows for...
the calculation of critical parameters and predictive performance. For scale-up and technology transfer, the CPPs are converted to scale-independent variables. Figure 3 shows an example of the design space (DS) for a spray dried product leading to particles of a desired morphology and size. Figure 4 shows a design of experiment (DoE) conducted for 'compound X' to identify the critical process parameters and critical quality attributes as part of process optimization and scale-up.

Effective implementation of models avoids reliance on a trial-and-error approach and provides critical information throughout drug product development. This leads to a robust manufacturing pathway and a thorough understanding to identify the CPPs and their impact on the CQAs.

These examples demonstrate that having fundamental mechanistic models based on engineering principles in combination with targeted process DoEs result in critical process knowledge and understanding, which in turn supports scale-up and technology transfer.

Conclusion

Successful technology transfer depends on many factors, including the ability to anticipate risks and plan ahead, so that the team is prepared to deal with all possibilities, including unforeseen events. It is important to connect the dots across the various elements of launch readiness (e.g., machines, manpower, materials, manufacturability, measurement, market, and mitigation) through utilization of a comprehensive risk management process.

Tools such as a readiness checklist, stage gate, governance, and visual boards can be used to develop an in-depth understanding of the process upfront, day-to-day focus on project requirements, clear escalation channels, and controls in place to ensure progress into each phase of the project. QbD principles are used to ensure process understanding and knowledge aid in the scale-up and transfer from development to commercialization, with CQAs and CPPs that can be closely monitored and controlled.

Forming a partnership and communicating effectively and transparently between sending unit and receiving unit is key, as is promoting continuous improvement and learning. PT
Jeff spent all day searching for a pharma supplier.

He should have visited Pharma Marketplace instead.

Pharma Marketplace is an online directory that connects you with 2,000 bio/pharmaceutical suppliers around the world.

Don’t be like Jeff.

pharmtech.com/marketplace
Locking Fraudulent Materials Out of the Supply Chain

Rita Peters

Supplier vetting and monitoring—plus comprehensive testing—ensure quality of raw materials.

The threats posed by counterfeit drug products entering the healthcare system and reaching patients have been well documented. The World Health Organization estimates that 1 in 10 medical products in low- and middle-income countries is substandard or falsified (1). A report based on 2013 data identified prescription drugs as the leading type of counterfeited products worldwide, exceeding fraudulent sales of electronics, food, auto parts, toys, clothing, and shoes (2).

Chances are, the inexpensive handbag or watch sold by a street vendor is not the authentic brand product; however, a knock-off fashion accessory will not cause the buyer physical harm. Substandard or falsified drugs can have serious health implications for patients, especially when fake drugs look like the real thing.

Regulators routinely warn consumers against buying drugs from unknown sources and have worked to shut down fraudulent online pharmacies. The Falsified Medicines Directive introduced by the European Commission and the Drug Supply Chain Security Act in the United States set standards for product identification and traceability for finished prescription drug products. Drug companies and contract manufacturers have made significant investments in packaging, labeling, software, and electronic monitoring systems to track drug packages throughout the supply chain. Materials such as edible taggants are proposed as options to track the drug product itself.

While these anticounterfeiting efforts are directed at the final drug product, bio/pharma companies must be vigilant for fraudulent or substandard materials at the other end of the supply chain: the raw materials used to make the drug.

Contaminated or substandard ingredients pose serious safety threats. Two examples, one from more than a decade ago and one that is ongoing, illustrate the vulnerability of the raw materials supply chain, shortcomings in quality control processes at drug companies, good manufacturing practice failures, flaws in regulatory oversight, and the need for improved test methods.

Suspect supply chain

Following reports in 2007 and 2008 of adverse reactions, including deaths, to the commonly prescribed blood thinner heparin, an investigation revealed that the patients received contaminated doses of the drug containing over-sulfated chondroitin sulfate (OSCS), an inexpensive synthetic adulterant. Regulators suspected that the OSCS was added to offset a shortage of heparin, which was in short supply due to a disease outbreak in pigs, the animal species used to source the material.

Regulators traced a complicated supply chain from a US-based firm to an affiliated China-based manufacturer, and the crude heparin supply chain in China. The supplier argued that existing GMPs and pharmacopeial testing standards could not detect, identify, or remove the substance (3). In response to the heparin crisis, the US and European pharmacopeias made extensive revisions to their respective heparin monographs.

Responsible for the unknown

The current contaminant case, which involves recalls of generic angiotensin II receptor blocker (ARB) drug products, began in mid-2018 when a generic drug manufacturer identified N-nitrosodimethylamine (NDMA), a probable human carcinogen, in an API supplied by China-based Zhejiang Huahai Pharmaceutical Co., Ltd.
(ZHP). Subsequent testing found N-nitrosodimethylamine (NDEA) in valsartan products and some irbesartan and losartan products; in March 2019, N-nitroso-N-methyl-4-aminobutyric acid (NMBA) was identified in losartan potassium products.

The agency suspects the impurity may have been generated by chemical reactions during the API manufacturing process, or from the reuse of materials, such as solvents.

While admitting that neither the industry or agency understood how NDMA or NDEA could form during the API manufacturing process, FDA clearly established that the responsibility for quality control is with the API manufacturer, stating: “It is the manufacturer’s responsibility to understand and assess their manufacturing process, assess any changes to that process, and based on that assessment and understanding, ensure test methods utilized can detect impurities expected to develop during the manufacturing process” (4).

The agency reinforced that message in a warning letter to ZHP in November 2018: “Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and that your process development study was adequate. We disagree. We remind you that common industry practice may not always be consistent with CGMP [current good manufacturing practice] requirements and that you are responsible for the quality of drugs you produce” (5).

Risk and responsibility
“The global nature of drug supply chains and manufacturing practices has evolved dramatically in recent decades,” says Jaap Venema, chief science officer at the US Pharmacopeia (USP). “This has made it necessary for all stakeholders involved in drug manufacturing to explore emerging areas of risk and identify where medicine quality may be vulnerable to being compromised.” FDA, USP, and other stakeholders must work together to develop best practices and appropriate predictive tools for understanding and addressing these risks, he says. “Recent industry disruptions around recalls and adulteration drive home the importance of knowing your suppliers and understanding their sources and suppliers of materials,” says Maxine Fritz, executive vice-president, Pharma BioTech, NSF International. “It’s essential to have a process that traces raw materials to origin and verifies the integrity of the system at every point along the way.”

The supplier must have product requirements that include the composition of the materials, as well as any product/process and/or material degradants or variability. In addition, manufacturers that rely on sole source suppliers are at the mercy of that supplier’s ability to deliver the materials as needed, says Fritz.

“Because of the complexity of the global excipient supply chain, it is often difficult for a pharmaceutical manufacturer to know the actual source of materials, or to have complete faith in the testing of critical quality attributes of a material, even from trusted suppliers,” says Catherine Sheehan, senior director, excipients, USP. Over time, suppliers may change production processes, organizational structures, distribution chains, or lab services.

“Routine identity testing of incoming materials and periodic supplier validation may help reduce risks,” she says.

The global scale and variety of suppliers for pharmaceutical raw materials creates complications for vetting suppliers, says Frederic Prulliere, Raman ID products manager, Agilent Technologies. “This leaves room for low purity, adulterated, counterfeited, or even harmful products to enter the drug manufacturing supply chain. Limited governmental oversight, multiple industry suppliers, and geopolitical events can all add to the challenge of supplying raw materials in the pharmaceutical industry,” he says.

The potential to receive counterfeit materials is greater for high value excipients, says Sheehan. “Some materials, like glycerin, have shown a high risk of economic adulteration. More than 800 deaths have been attributed to multiple glycerin adulteration events within the past century,” she reports. “Without proper testing, substandard or even poisonous substances can then enter the pharmaceutical supply chain.”

It is imperative that pharma companies follow 21 Code of Federal Regulations 211.84(d)(1) (2), which mandates full identity testing for all incoming lots of drug product components, Sheehan recommends. If a supplier’s certificate of analysis (CoA) is used in lieu of analysis of other attributes, that supplier’s test results should be regularly validated by the pharma company.

While the potential for introducing adulterated materials in the pharmaceutical supply chain is real, companies with a risk-based approach to incoming raw materials inspection are unlikely to use counterfeit or adulterated products, says Prulliere. “Controlling the quality of the raw material before it enters production, qualifying and vetting suppliers, assessing and managing risks, and tolerance for these risks are the quality pillars that pharmaceutical companies should implement to deal with this potential,” he says.

Supplier oversight and inhouse analysis
Current standards should help pharma companies identify counterfeit materials before they enter production, says Sheehan; however, not all pharma companies are applying this standard consistently and performing identity testing on each lot of incoming raw materials, including excipient raw materials. “Occasional or skip lot testing or reliance on a supplier’s CoA is inadequate,” she says, noting that FDA cited 20 different firms in 2018 for failure to adequately test incoming raw materials.

Many, but not all, drug manufacturers are testing for substandard materials, which is concerning from a public health standard, says Fritz.

“A certificate of analysis is a strong reassurance, but a certificate is only as good as the testing performed, the qual-
Supply Chain: Raw Materials

ity oversight, and the quality systems that the supplier has in place,” says Fritz.

“A company can’t watch raw materials being produced, load them in a truck, and transport them to their factory. Using a robust supplier qualification that includes routine inspection and verification will help to lower risk and increase confidence in the quality of incoming raw materials,” says Sheehan. “However, routine material analytical testing of each incoming lot using a USP documentary standard and associated reference standard, if available, provides a final quality check and safeguard to help ensure only acceptable materials are released into production.”

Ideally, pharma manufacturers should test for critical quality attributes, but at a minimum they must perform a full identity test for all incoming lots of components, she says.

“Using PIC/S [Pharmaceutical Inspection Co-operation Scheme] guidance, quality control labs are only required to identify raw materials provided a supplier evaluation program is in place. If not, a full analysis is usually conducted,” says Prulliere.

Mid-infrared, near infrared, or Raman spectroscopy are typically effective for verifying incoming raw materials due to probing the vibrational modes of a material providing a structure specific spectrum, he says. “Spatially offset Raman spectroscopy (SORS) is gaining popularity. SORS extends the depth of penetration to eliminate container contribution to the measurement and permit analysis through non-transparent containers.”

A third-party supplier verification service can be used to ensure suppliers are adhering to a culture of quality, follow appropriate CGMP regulations, and produce materials that pass random lot analytical testing at regular intervals, says Sheehan.

“Incorporating this verification plan within a quality standard operating procedure may help pharma manufacturers comply with FDA supplier validation requirements for using CoA data,” she says.

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Continuous Manufacturing — contin. from page 38

Whether frequent changeovers can be performed efficiently to enable short duration runs and small batches is still an open question. While a desired goal is to be able to changeover in less than a day, current lines can take a week or more for changeover due to the extensive time for disassembling, cleaning, and reassembling. Improving changeover time is an ongoing process, and future facilities may benefit from making cleaning part of the initial equipment design (4). Early adopter Vertex and its contract manufacturing partner Hovione have improved changeover time by, for example, optimizing the order in which parts are disassembled and cleaned and by identifying spare parts, such as filters, that can be switched on the fly. Vertex has also created a library of operator training videos to aid reassembly (5).

Pfizer is moving forward with its Portable Continuous Miniature and Modular (PCMM) system using GEA’s Consigma processing system, which can be installed in a “podular” facility using G-CON POD prefabricated cleanrooms. The system is designed to be flexible for meeting market demand. The podular technology enables quick installation in a location and the ability to move the system to another location if necessary. Pfizer installed its first PCMM unit in Groton, CT in 2015, and the same processing equipment in Freiburg, Germany in 2018. Pfizer is working to develop computational models of the system’s in-line powder mixer that are being used for process development and optimization. As one example, the models are being used to optimize the line startup process (6).
There is a significant opportunity for digital technology to improve quality and efficiency in pharmaceutical manufacturing. Life-science organizations that replace paper-based processes and siloed systems with modern digital applications are better positioned to meet current and future drug manufacturing demands, especially as the industry embraces precision medicine and treatments become more individualized.

The pharmaceutical manufacturing plant floor is ripe for digital transformation, where it can enable operators to quickly find current information and gather data in real time for smarter decision-making. Organizations are moving to modern cloud solutions to connect people, processes, and technology for greater agility and efficiencies. With a digitally connected facility, operators can use mobile devices to enter quality data or access the right information at the right manufacturing station at the point of need.

**Precision medicine is transforming supply chains**

In 2018, FDA approved 62 new therapeutic drugs, of which 25 were personalized medicines (1). This emerging approach to disease treatment targets a patient’s unique molecular and genetic profile and requires changes in the way that products are manufactured. Precision medicines are typically made for small groups of people with hard-to-treat illnesses and can be complicated to produce and difficult to scale.

Additionally, with many precision therapies, the patient becomes an integral part of a highly specific end-to-end manufacturing process. For example, with chimeric antigen receptor (CAR) T-cell therapy, approved for relapsed and refractory leukemia and lymphoma, the patient’s cells are collected at the hospital, shipped to a manufacturing center for engineering to target the person’s specific cancer, and then sent back to the hospital for infusion into that patient.

Traditional, large-scale drug manufacturing processes are not aligned with this highly individualized approach. The success and scalability of personalized medicine requires new strategies for automation and improved workflows to produce them reliably, safely, and economically.

**Opportunity for change on the manufacturing plant floor**

Today, much of the information on the pharmaceutical manufacturing floor is buried in paper binders or siloed applications. Without centralized systems for tracking and distributing content and intuitive applications that offer easy access, operators cannot quickly access the right information they need to perform their jobs and increases compliance and quality risks. Significant overhead is required to ensure that work instructions, standard operating procedures, and other information workers need to perform their jobs remain up-to-date and accurate.

If there are systems in place, they are disconnected. As a result, business process gaps between quality management systems (QMS) and content management applications develop, making it challenging to deliver quality products effectively.

Additionally, companies may try to get as much value as they can from their quality management and
manufacturing systems by operating them way past their shelf life. This practice can actually increase costs because aging systems tend to be over-engineered and customized, ficer at Samsung BioLogics. “Delivering content directly to manufacturing stations through a mobile application will make it faster for teams to stay up-to-date.”

**Success and scalability of personalized medicine require new strategies for automation and improved workflows to produce them reliably, safely, and economically.**

and require frequent maintenance. Older systems are often too rigid to adapt to new processes, manufacturing or training methods, or production requirements, and they cannot efficiently scale down for small batch production.

The life-sciences industry has continued to lag other industries in adoption of new technologies. In a recent survey by Deloitte with MIT Sloan Management Review, only 20% of biopharma companies are maturing digitally (2). Leveraging modern solutions to enable timely delivery of information to the plant floor and tying real-time data with quality management systems can improve agility and help manufacturers meet requirements for innovative therapies such as personalized medicines.

Companies like Samsung BioLogics, a large contract development and manufacturing organization for biologics, are taking a fresh approach to ensure that they remain efficient and agile as they scale. Leveraging modern technology and its parent company’s manufacturing expertise and experience, Samsung BioLogics is progressively building larger and more advanced facilities that can run continuously 24 hours a day, seven days a week. “It’s challenging to manage and maintain information on the manufacturing floor and ensure operators are working from the latest procedures,” said James Choi, chief information officer at Samsung BioLogics. “Delivering content directly to manufacturing stations through a mobile application will make it faster for teams to stay up-to-date.”

**Centralized and more complete data**

A connected shop floor has the potential to improve productivity and enable better decision-making. Managers track how content is consumed at each facility, station, and device, and update the content on an as-needed basis. This functionality offers a new lens into the effectiveness of the content. For instance, managers can measure whether document-based instructions are performing better than a short instructional video by measuring the impact on compliance and quality.

Video is gaining popularity as an effective training tool. Delivering video through mobile devices directly on the shop floor can dramatically improve manufacturing efficiency and compliance. Managers see how employees are engaging with the content that is delivered digitally to each station and, using that data, design instructions and training modules that fit best with that particular task or even with a particular employee’s learning style.

**Going mobile for greater plant agility**

Mobile devices such as tablets are ideal for collecting and distributing real-time information to the plant floor. Using tablets, operators and technicians can deliver updated content and collect data that can be analyzed for improved visibility and efficiency. Cloud applications that were designed specifically for the manufacturing plant floor can be run on mobile devices and support manufacturing processes with up-to-date content and seamless integration with quality management systems.

Synchronizing content on mobile tablets at each work station has many benefits. First, the content is completely accessible to operators, and also available for offline viewing. This prevents them from having to page through stacks of paper to find the right instructions.

Second, mobile applications provide real-time visibility into quality events, allowing manufacturing and quality teams to address and resolve issues quickly when they first come to light, before they have a bigger impact. For example, with a tablet, workers can detect deviations right on the plant floor and enter them immediately at the point of observation, permitting rapid triaging, impact assessment, and remedial action as quickly as possible.

**Training for optimal quality management**

A connected shop floor supports training methods that provide the flexibility and versatility needed in modern manufacturing. Information, such as
relevant digital procedures and work instructions, can be presented to workers at specific points in the manufacturing process, reducing complexity and, with it, variation.

This targeted learning approach is replacing passive “read and understand” instructions, ensuring that employees master the procedures most important to their jobs. Companies can expect better results from training programs that are shifting from individual, content-driven events to learning that is deeply contextual, social, and embedded into the flow of everyday work. This approach ensures that individuals are not just qualified but also prepared to do their jobs.

Training platforms that apply these techniques are catching on in the life-sciences industry. By connecting learners with training content at the time of need and according to specific learning styles, companies can change behaviors to decrease quality events. Mapping training content to learner roles based on job functions, then delivering it through a role-based, content-centric experience simplifies training, while making it more cohesive and integrated with quality goals.

**Quality 4.0 and the rapid detection of quality events**

Quality 4.0 comes from Industry 4.0, and is typically defined as the adoption of new technology to improve operational efficiency and product quality. It can simplify processes and speed up manufacturing while enhancing compliance and quality. Connecting the plant floor with mobile devices and cloud-based applications is a prime example of Quality 4.0 in action. Almost 60% of biopharma managers say that digital is a top priority, and they expect to realize the value of their investments within the next five years (2).

A modern QMS provides transparency for greater collaboration among employees and suppliers. Information shared with partners builds alignment and progress toward common goals. Further, connecting operational data allows proactive risk management by addressing quality issues before they arise, as well as by providing real-time quality data for analysis to increase productivity and allocate resources based on risk and need.

**Seamless integration with MES, ERP, or PLM across the value chain**

Quality 4.0 enables a quality system to integrate seamlessly with a manufacturing execution system (MES), enterprise resource planning (ERP), or product lifecycle management (PLM) system across the value chain for a more holistic view. For instance, connecting a QMS with a MES enables rapid detection, triaging, and remediation of non-conformances. When a MES detects a potential non-conformance, it promptly sends the information to a QMS. The quality team can then quickly evaluate, remediate, or resolve the non-conformance.

With a more connected environment, including on the plant floor, pharmaceutical manufacturers can build stronger relationships internally and externally with systems that track, engage, and facilitate communication and problem-solving in real-time.

Quality 4.0 doesn’t mean adding layers of technology or customized systems to manufacturing processes that are already overloaded. Instead, the approach simplifies systems and reduces complexity. A simplified environment supports both standardization and harmonization through streamlined processes that eliminate siloes and other roadblocks to managing quality in manufacturing. Standardization is one process to deliver quality products efficiently on a global scale, while harmonization allows for regional variability and flexibility.

**The future of quality in pharmaceutical manufacturing**

Quality 4.0 is becoming a reality in pharmaceutical manufacturing as companies adopt new technologies to improve operational efficiency and product quality, and adapt to the manufacturing of precision medicines. Adopting Quality 4.0 for a connected shop floor enables manufacturers to gain real-time visibility across content and quality management processes for better tracking and more meaningful and actionable insights.

Transforming quality management is key to successfully scaling production of new therapies and is ripe with opportunities. Next-generation solutions that emphasize flexibility and efficiency position manufacturers to reap enormous benefits in simplifying and improving quality management. Samsung BioLogics is already seeing a positive impact with its modern approach, which is reducing product switching time and enabling greater agility as it scales.

As companies shift to multi-product lines, they need to be more nimble. To meet current and future needs of patients, life-science companies can enable processes that are flexible and always compliant. Eliminating siloed systems in favor of streamlined solutions allows for greater agility and stronger collaboration while enhancing compliance and end-to-end control. This will help enable life-science organizations to meet the new demands of quality management in manufacturing and help support innovation in precision medicine.

**References**


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Non-medical complaints do not need to be reported to the regulatory authorities, but they should be documented and investigated. These types of complaints (e.g., smashed bottle, smashed carton, incorrect tablet count, etc.) do not need to be reported to regulatory agencies, but they still need to be investigated as they could indicate deficiencies in the manufacturing and packaging operations. There are other considerations to consider when establishing a complaint handling function, such as whether or not the company wants to try and have the product returned for examination and how the product will be handled if it is procured. Keep in mind, however, that all complaints are available for regulatory review during an inspection.

Establishing a robust and well-documented complaint handling process is a significant and important element of a strong quality system. Thought and consideration on how complaints will be communicated to the rest of the organization and how complaint resolutions will be investigated, documented, and reported are critical elements to having a complaint function that serves the organization, the customers, and the regulatory authorities.

References
2. FDA, 21 CFR 211.180 (e)(2), Current Good Manufacturing Practice for Finished Pharmaceuticals, Records and Reports, April 1, 2018.
3. FDA, 21 CFR 211.198, Current Good Manufacturing Practice for Finished Pharmaceuticals, Complaint Files, April 1, 2018.
A robust customer complaint handling system is an integral part of a quality management system, says Susan Schniepp, executive vice-president of post-approval pharma and distinguished fellow, Regulatory Compliance Associates.

Q. I am a quality assurance professional working for a small start-up company. I am setting up their quality management system, but I have little experience with complaint handling. Can you provide some basic advice on setting up a system to handle customer complaints?

A. A complaint handling system is a critical quality function that needs to be designed in conjunction with your quality management system (QMS). The requirements for complaint handling are well documented in the regulations (1–3). The importance of the complaint system and its relationship to other functions is often underappreciated by companies when setting up a QMS. The complaint system should be one of the first systems to be established by a company because the information gleaned from complaints feeds directly into the deviations, investigations, and corrective actions and preventive actions (CAPA) functions. Whether your product is a prescription drug (small or large molecule), over-the-counter medication, medical device, or combination product, the process for addressing complaints falls under regulatory scrutiny (4).

The first element of a robust complaint system is to establish a standard operating procedure (SOP) for complaint handling. The SOP should indicate the communication vehicle used to collect customer complaint information. These communication avenues can include, but are not limited to, use of a dedicated telephone number and/or an Internet link where customers can report the problem they are having with your product. It may seem archaic to recommend a phone number, but it is necessary because not everyone taking your medication is comfortable with or has access to the Internet, and these individuals may be more at ease leaving a message on an answering machine. Needless to say, this is an element of the complaint handling system that might be outsourced. If you decide to outsource this activity, you should specify this in your SOP and have a quality agreement with the company that is performing this service for you.

Once the basic communication elements are determined and established, they need to be monitored on a routine frequency. The monitoring frequency should be established in the SOP for the handling of complaints. The phone line and the web link should be monitored at a minimum once a day. It would be ideal if the communication lines could be continuously monitored, but this may be impractical for a small company. If this activity has been outsourced, the information collected on a daily basis by the service provider should be collected and reviewed on a daily basis by the company.

The next element needed for effective complaint handling is determining the information that you need from the customer. At a minimum you will want to know (4):

- Name and contact information
- Age and sex
- The name of the product
- The dosage strength, if applicable
- The name of the store where the purchase was made
- A detailed description of the problem/issue associated with the product.

Again, if you are outsourcing this function, you will need to make sure this information is being collected by your service provider.

Once you have established the communication avenues and the information requirements, you need to determine the complaint categories. There are several complaint categories that a customer might want to report to a company including medical conditions, product quality problems, preventable mistakes, and therapeutic failures. Any type of medical complaint is serious and needs to be assessed and addressed in a timely manner, because these types of complaints often have regulatory reporting timelines associated with them.

Medical complaints can range from mild (e.g., headache, rash, tiredness, etc.) to serious reactions (e.g., hospitalization, suicidal thoughts, death, etc.). The more serious the medical complaint, the more aggressive the company needs to be in pursuing the investigation into the complaint. The regulatory reporting requirements for medical complaints should be specified in the SOP.

It would be ideal if the communication lines could be continuously monitored.

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