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Director of Quality Systems
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Phil Borman, DSc
Director, Product Development & Supply
Medicinal Science & Technology
Pharma R&D

Evonne Brennan
European Technical Product Manager, Pharmaceutical Division, IMCD Ireland

Tim Freeman
Managing Director
Freeman Technology

Filipe Gaspar
Vice-President, R&D
Hovione

Rory Budihandojo
Director, Quality and EHS Audit
Boehringer-Ingelheim

Christopher Burgess
Managing Director
Burgess Analytical Consultancy

Ryan F. Donnelly
Professor
Queens University Belfast

John Pritchard
Technical Director
Philips Respironics

Rory Fitzsimmons
Professor, Research Chair in Formulation Design and Drug Delivery, University of Copenhagen

Clifford S. Mintz
President and Founder
BioInsights

Tim Peterson
Transdermal Product Development Leader, Drug Delivery Systems Division, 3M

Roderick J. Rumsey
PhD
Director, Product Development, 3M

Roni Shattuck
Managing Director
Multimedia Healthcare

Barbara Williams
Sales Operations Executive

F. Michael Tracey
Sales Manager

Dr. John E. Pritchard
Professor
Queens University Belfast

Evonne Brennan
European Technical Product Manager

Maximilian Heider
PhD
Director, Product Development

Kerenford von Winternitz
CEO

Jim Miller
CEO

John Pritchard
Technical Director

Philips Respironics

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Multimedia Healthcare

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F. Michael Tracey
Sales Manager

Dr. John E. Pritchard
Professor
Queens University Belfast

Evonne Brennan
European Technical Product Manager
The United Kingdom put its left leg in Europe, is now trying to pull its left leg out, and as the well-known song goes, is seemingly ‘shaking it all about’ with a lack of clear direction and much confusion over potential future relationships. But what impact will this Brexit ‘hokey cokey’, that is presently underway, ultimately have on the bio/pharma industry?

According to the original timeline, the UK should have already left the European Union—initially scheduled to happen on 29 March 2019. However, with the UK Parliament at an impasse, there is uncertainty over whether the UK will leave the EU with any deal whatsoever.

**No deal, no drugs?**

So, if the UK leaves the EU without a deal in place, what does that mean for the bio/pharma industry? As Lynn Byers, executive director for NSF International, explained back in November 2018, if the outcome is ‘no-deal’ then the UK becomes a third country, which will impact many aspects of the bio/pharma market for both the UK and Europe (1).

Some of the areas that will be affected in a ‘no-deal’ scenario include batch release and testing, imports and exports, regulatory issues, packaging, and clinical trials. Byers highlighted packaging as the aspect that will probably incur the most significant impact and as the one facet that may not have been considered by many companies in their Brexit preparations. “If you change a batch release site, your qualified person, and your marketing authorization number, the packaging will be affected,” Byers confirmed. “All the artwork will need to change, and everything will need to be repackaged, which is a substantial issue.”

Add to this the anticipation that the value of the British pound will fall in the event of a ‘no-deal’ Brexit and, as the Association of the British Pharmaceutical Industry (ABPI) noted, there may be knock-on effects for patient access to medicines due to preferential exporting. In light of this potential issue, the ABPI has called on the government to place a temporary ban on drug exports by wholesalers to protect the National Health Service from prospective drug shortages (2).

**Contingency planning**

Both sides, the UK and Europe, have issued documents listing important steps companies should be considering in order to prepare for every potential Brexit outcome, particularly a ‘no-deal’ scenario. For example, the European Medicines Agency (EMA) recently published a questions and answers document assuring that drug safety will not be impacted by Brexit (3), and the UK’s Medicines and Health products Agency (MHRA) has laid out a new process for regulatory submissions in a ‘no-deal’ Brexit scenario (4).

Despite the planning made by industry, however, there are many issues that fall out of its control that will still significantly impact the flow of medicines between Europe and the UK. As reported in *The Financial Times*, factors such as congestion at ports and regulations cannot be predicted until there is clarity over the way in which the UK will leave the EU (5).

Furthermore, investment in the bio/pharma sector is expected to be impacted, which itself could affect access to medicines. *The Guardian* reported that AstraZeneca, which is not alone in its actions, has frozen manufacturing investments, and Eisai has confirmed it will not make any new investments in the UK until there is clarification on the Brexit situation (6).

**An anxious wait**

The UK’s Prime Minister, Theresa May, herself stressed the importance of the pharma sector in her national campaign launch speech back in July 2016 (7) when she said, “It is hard to think of an industry of greater strategic importance to Britain than its pharmaceutical industry.” Yet, despite these sentiments, and repeated calls from industry to avoid a ‘no-deal’ scenario at all costs, the sector is still facing an anxious wait on the eventual outcome of Brexit.

On a final note, there may even still be a second referendum or complete reversal to Brexit, with a significant number of people (six million) calling for Article 50 to be revoked (2). So, if the finale of this long-drawn out process is Brexit being turned around, as the ‘hokey cokey’ suggests, is that what it’s all about?

**References**


Felicity Thomas
Editor of Pharmaceutical Technology Europe
FThomas@mmhgroup.com
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Regulating Pharmaceuticals in the Environment

The European Commission has published a strategy that will form the basis for the European Union’s policy on pharmaceuticals in the environment.

After several years of consultations with stakeholders followed by periods of prevarication, the European Commission has finally published a strategy (1) that will provide a basis for the European Union’s policy on pharmaceuticals in the environment (PIE). The commission has been obliged to draw up the strategy under two pieces of EU legislation—one introduced more than eight years ago on pharmacovigilance (2) and the other approved in 2013 on water pollution (3). It had also pledged to issue a PIE policy under agreements with the United Nations and other international bodies.

The publication and contents of the strategy were welcomed by a joint PIE task force of the three main European pharmaceutical trade associations. The strategy covers several areas on which the task force itself and other industry initiatives are working, such as the identification and prioritization of medicines likely to present environmental risks, more effective monitoring of environmental impacts, and greater data transparency with environmental risk assessment (4).

The industry is broadly supporting the strategy despite the likelihood that it could result in tougher PIE regulations. “There are many things in the strategy that are good, although there are others that we are concerned about,” Bengt Mattsson, co-chair of the joint task force, told Pharmaceutical Technology Europe. “On the whole, it is a positive document that will allow us to be closely involved in continuous discussion among stakeholders about the best way forward on the PIE issue.”

Six key areas

The strategy was issued by the commission as a ‘communication’ so that it did not have to be a vehicle for presenting specific proposals for legislation. Instead it pinpoints six areas for possible regulatory and other measures to tackle what it calls the ‘emerging problem’ of pollution by pharmaceuticals and their residues.

The six areas listed in the strategy are increasing awareness of the PIE issue, filling knowledge gaps about the problem, promoting greener manufacturing, and the development of medicine less environmentally harmful, improving environmental risk assessment, expanding environmental monitoring, and more efficient waste management (1).

Any new PIE regulations—in the form of new legislation or amendments to existing regulations—may not come into force for several years because of the necessity for further consultations and other preparatory work, such as social and economic impact assessments necessary for legislative changes. Any legislative action would have to be put forward by a new commission, which is due to take office in November 2019 (5). Also, there will be uncertainties about the environmental stance of a new European Parliament, which is scheduled to be inaugurated in July 2019.

Until the two arms of the legislature are actually presented with draft regulations by the commission, the arguments about the most effective ways of dealing with pharmaceutical pollution will continue to rage among the major stakeholders—such as the pharma industry, regulators, healthcare professionals, and providers and non-governmental organizations (NGOs).

However, as a result of the publication of the strategy, the scope of the discussions will be much narrower—at least in terms of what steps can be taken with the strong support of the EU at the regional and national levels. “At least we know what will now be the focus of the discussions as laid down by the range of options selected in the Commission’s strategy,” said Mattsson.

Filling knowledge gaps

A priority will be the creation of research projects to help fill, through the EU-funded research programme, a variety of knowledge gaps. The EU has already financed in recent years at least 10 research projects on pharmaceutical pollution and waste treatment processes.

“More information is still needed to understand and evaluate certain pharmaceuticals [regarding] their environmental concentrations and the resulting levels of risks,” said the commission in the document (1). It admits that ‘no clear link’ has been established between pharmaceuticals in the environment and direct impacts on human health. But it points to a World Health Organization study showing possible effects of long-term exposure to vulnerable populations that dictate a need for a precautionary approach to the PIE problem (6).

Also, there are worries about the role of the environment in antimicrobial resistance (AMR), on which the commission has already launched an action plan (7). The PIE strategy highlights the ‘particular concern’ that emissions from some antimicrobials manufacturing plants in third countries, some of which export products to the EU, could be contributing to AMR’s global spread.

Research, including that in areas like AMR, will be a major objective of the strategy through EU-funded programmes and organizations like the Brussels-based Innovate Medicines Initiative (IMI), which has a €5-billion (approximately $5.6 billion) budget provided jointly by the EU and the pharma industry. Among the IMI’s projects is a scheme called Intelligent Assessment of Pharmaceuticals in the Environment (iPIE), which conducts research to help support regulatory initiatives.

“The industry has a lot to contribute because we should know more about our substances than others,” explained Mattsson. But he also pointed out that the other stakeholders would be
heavily involved in discussions on future measures, covering the whole lifecycle of pharmaceuticals.

Among the research mentioned in the strategy are schemes to support the development of ‘greener’ pharmaceuticals, which degrade more readily in wastewater treatment plants and in the environment. Also, research can be used to manage risk more effectively by increasing knowledge, for example, on the eco-toxicity and environmental fate of pharmaceuticals. Another research aim would be to find out more about the effects on humans of chronic exposure to low levels of pharmaceuticals in the environment, taking into account mixtures of multiple pharmaceutical substances.

Greener processes
A combination of regulatory pressures and incentives could be used to persuade pharmaceutical companies to switch to more environmentally benign medicines. For example, procurement policies could be more widely applied to encourage greener pharmaceutical design and production processes.

A more fundamental move would be “to explore how extended producer responsibility could play a role in supporting action to improve the efficacy of water treatment,” according to the commission.

As pharmaceuticals and their production processes become greener, regulations could be changed to target more pharmaceutical substances considered to be an environmental risk. Under the Water Framework Directive (WFD) (8), the EU’s main legislation on preventing water pollution, pharmaceuticals with similar effects could be put into risk categories limiting their water concentrations.

Under the Industrial Emissions Directive (9), the primary legislation for applying pollution controls on pharmaceutical manufacturing plants, state-of-the-art production processes may have to be employed in the production of certain medicines and active ingredients.

The strategy document even suggests that the EU exert its influence through ‘dialogue and co-operation’ to encourage non-EU countries to take action on pharmaceutical emissions from plants suspected of contributing to global AMR.

Expanding environmental monitoring
Among other key strategy options is raising the efficiency of environmental monitoring of pharmaceuticals and improving their risk assessment. It suggests increasing environmental expertise among regulators involved in environmental risk assessment of medicines. Ways should be examined of giving the public more access to information from environmental risk assessments and relevant toxicological thresholds, while taking into account data-protection rules.

To expand monitoring, the commission will consider adding more pharmaceuticals to the WFD’s ‘watch list’. Also, it will support studies on the monitoring of pharmaceutical substances not only in fresh and marine waters but also in soils, sediments, and wildlife.

The feasibility of monitoring of AMR microorganisms and genes could be considered, including their inclusion in the EU’s Europe-wide survey of soil conditions with observations being made at 250,000 sample points.

Industry warning
As the EU prepares to become much more active in controlling pharmaceuticals in the environment, industry is warning that regulatory and other initiatives must be based on science and risk. “We are worried that general limits on concentrations of pharmaceutical substances will be imposed, which are not justified on the basis of science or risk,” Mattson explained. “We don’t want pharmaceutical substances to be banned or restricted just because they are hazardous without taking into account risks of exposure. Medicines are intrinsically hazardous, otherwise they would not have beneficial effects on patients.”

Nonetheless the commission says in the strategy document that it will foster exchange of information between EU states on best practices in taking environmental considerations into account in ‘the choice of therapy’. Also, it will consider the findings of recent evaluations of chemicals under the EU’s Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) legislation (10) on chemicals safety “as regards links with medicinal products legislation in relation to environmental protection.”

Currently, pharmaceutical substances, except intermediates used in production, are exempt from REACH regulations. There is a danger that as the EU subjects medicines to more environmental controls, the long-established divide between medicines and environmental regulations will start to become blurred and there could be a conflict of interests between the two.

References
Patient-Centric Drug Development Comes of Age

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 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,
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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."

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,

**Spray drying: Supporting patient-centric drug development**

There are multiple issues, including solubility, that can plague drug development. As more poorly aqueous soluble compounds are entering development, industry is witnessing increased popularity in a range of techniques that may overcome solubility issues.

One such technique is spray drying, which is expected to experience continued growth as a result of efficiency rates and improvement in stability of products (1). To learn more about spray drying and how it can support patient-centric drug development, Pharmaceutical Technology Europe spoke with Manuel Leal, business development director for Spanish contract development and manufacturing organization, Idifarma.

**PTE:** Can you briefly overview spray drying and how it may be used to overcome specific formulation challenges?

**Leal (Idifarma):** Spray drying offers a unique solution to some of the most demanding formulation challenges posed to the pharmaceutical industry, such as solubility, stability, and bioavailability.

It involves spraying a solution or suspension that contains the active substance and the corresponding excipients inside a drying chamber. As the solvent is evaporated at high speed, dry particles are dispersed and collected by a cyclone. Particles obtained after spray drying are amorphous solid dispersions with different particle sizes, achieving better solubility than the API alone.

Around 40% of all new chemical entities (NCEs) have low water solubility, meaning a strategy for improving poor bioavailability becomes mandatory.

There has also been a growing difficulty to find new drugs that improve existing therapies, therefore the need to use innovative processes, such as spray drying, to advance the galenic formulation of the finished product is vital. Using such technologies means the industry is no longer reliant on finding new active molecules.

**PTE:** What are the benefits of spray drying over other technologies/solutions?

**Leal (Idifarma):** Spray drying operates on a continuous production process; therefore, batch size is not limited by the equipment capacity common with other technologies. This means that spray drying presents a scalable and cost-effective solution as it is a rapid and easily repeatable process.

Spray drying lends itself more favourably to certain drug products. The technology allows control over particle size and morphology in one single process, which is particularly useful for drugs for inhaled administration. It also suits temperature sensitive molecules, as the product spends less time exposed to heat compared with other processes.

**PTE:** How can spray drying support patient-centric drug development/formulation?

**Leal (Idifarma):** Spray drying can support patient-centric drug development in a variety of ways, from modifying the release of the active substance to changing the administration route to aid patient compliance.

Adherence or compliance problems are apparent within many chronic therapies, which might result in a lower therapeutic effect of the treatment. Yet, the development of dosage forms allowing a prolonged release of the active substance can improve therapeutic compliance by reducing the number of times a patient has to take the medication.

Enhancing a dosage form is even more relevant with intravenous pharmaceutical forms, because of the reduction of needle punctures the patient needs to receive in long-term treatments. Spray drying enables the manufacture of modified release intermediates for several pharmaceutical forms including tablet, capsule, powder inhalation, and IV solutions.

Another interesting application is that spray drying can facilitate different administration routes by changing the pharmaceutical form of the finished product. By improving the solubility and bioavailability, drugs with parenteral administration could be administered by oral route. This improves comfort for the patients, allowing them to take the drugs at home. Plus, the costs associated with the administration of a product at a hospital and manufacturing sterile products are avoided.

The benefits of this technology are particularly compelling for orally administered drugs because more problems related with this route can be resolved. One way is that drugs that had been incompatible with food intake can be encapsulated and released in another part of the gastrointestinal tract, avoiding the food effect and simplifying the delivery of the drug for the patient.

In addition, with the microencapsulation of the active substance, a lower degradation of the drug at a gastric level can be reached and so, in some cases, it is possible to lower the strength administered to the patient.

And finally, spray drying can also support patient compliance through taste-masking, as bad tastes are common in a lot of active substances. Overcoming this using spray drying technologies can also directly impact the comfort of the patient taking the product, and therefore, in therapeutic compliance.

**PTE:** What specific requirements are important when selecting a spray drying partner?

**Leal (Idifarma):** As well as the standard requirements, such as experience, competitive costs, and corresponding official certifications, there are additional aspects to consider when selecting the right spray drying partner.

Companies should take into account a potential partner’s ability to work with a specific profile of molecules (particularly that of highly potent molecules), whether they can handle the required volumes, and if they have the capacity to perform galenical trials, as these are all important factors.

Any chosen provider must have a flexible corporate structure and be experienced in project management, so they can easily resolve problems using their experience and capabilities in complex pharmaceutical developments. They should also look for a provider who does not have its own portfolio of products to avoid any potential conflict of interests.

**Reference**

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 the 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 paediatric 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 paediatrics, there was general agreement that most conventional drug delivery systems are not ideal. “Paediatrics 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 programme 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 programme 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 the US Food and Drug Administration (FDA) in the United States, under the 21st Century Cars 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 medical 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 paediatric studies for cancer drugs directed at relevant molecular targets,” he confirms. “The law will come into effect on 18 Aug. 2020. As a result, many paediatric 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**


PTE
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. The US Food and Drug Administration (FDA), along with other regulatory agencies, have taken steps to address this particular issue (2,3). Drug makers need to consider approaches 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.

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.”

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.”

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

Select Suppliers with Demonstrated Expertise to Avoid Sourcing “Bad” APIs
Confidence in the quality systems and scientific competence of the API manufacturing team is essential.

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

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identify whether there is a risk of formation of impurities that may fall under International Council for Harmonization 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, is it 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 cost-pointing of view, without any guarantee that problems will be avoided in the future,” he states.

References
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 haematopoietic 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.
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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 roads 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 sulphate 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 biological 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**

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.

Degradation Pathways: A Case Study with Pegylated L-Asparaginase

Chintan Patel, Sanjay Bandyopadhyay, and Gayatri Patel

PEGylation 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-asparagine 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/
The tetrameric structure of the L-asparaginase enzyme is required for enzymatic activity (11). Pegaspargase (pegylated L-asparaginase) is a covalent conjugate of 4-\(\text{o}l\)-derived L-asparaginase with monomethoxypolyethylene glycol (mPEG) succinimidylic succinate (PEG-SS; molecular weight of 5000 Da). Approximately 69 to 82 molecules of mPEG are linked to L-asparaginase. The succinic linker between PEG and L-asparaginase contains an ester linkage that can lead to hydrolytic removal of the PEG moiety 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 4-\(\text{o}l\)-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-hydroxysuccinimidylic ester) at different sites of the \(\omega\)-NH\(_2\) group of N-terminal residue and \(\epsilon\)-NH\(_2\) 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-\(\mu\)m 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 \(\mu\)L 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.: ULT1740-3-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 \(\mu\)m). 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 \(\mu\)g of sample was injected and analyzed in isocratic 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 barium 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 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 (stored under 2–8 °C); 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. Chromatographic
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profiles obtained with samples of pegaspargase analyzed by HP-SEC followed by RI detection 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 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 and analyzed by HP-SEC followed by detection by an RI detector to check the effect of high temperature on release of PEG from the PEG-protein conjugate. 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 probably indicates conformational changes in 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

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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 approximatively 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 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 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**

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**Chintan Patel** is a researcher, and **Sanjay Bandyopadhyay, PhD**, is vice-president, both in the Department of Biotechnology, Zydus Research Centre, Cadila Healthcare Ltd., Ahmedabad, Gujarat, India; **Gayatri C. Patel**, M.Pharm, PhD, is associate professor in the Department of Pharmacetics & Pharmaceutical Technology, Ramnabhai Patel College of Pharmacy at the Charotar University of Science and Technology, Changa Campus, Changa- 388 421, Anand, Gujarat, India, gayatripatel. ph@charusat.ac.in, +91 2697 265162.

*To whom all correspondence should be addressed.*
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). 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 centred 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 solutions while most resins have good chemical compatibility. The chemical compatibility allows resins to be stored in caustic solutions, which can be beneficial due to their antimicrobial properties. Lastly, carbon content is variable (but mostly negligible) from resin to resin compared to proteins.

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 Processes

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).

Table 1: 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>

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 centres 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
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.

Results and discussion. Sodium hydroxide (NaOH) is commonly adopted as the cleaning agent for removing resin residues from the surface. This cleaning agent primarily uses the mechanism of solubility of the solute in NaOH at the temperature cleaned. When a formulated cleaning agent is used, the cleaning mechanisms to remove the residue from the surface may include solubility in an aqueous solution, wetting, emulsification, dispersion, chelation, and hydrolysis (14). These additional cleaning mechanisms are important in removing water insoluble residues from the surface. A formulated cleaner containing potassium hydroxide was successful in cleaning resin residues using 1% v/v cleaning solution at 45 °C up to 60 °C for 48 hours. Sodium hydroxide was not successful in cleaning resin residues. Sodium hydroxide was not effective in cleaning the residue and may be added as a secondary step particularly for mineral-based resins.

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OSD Continuous Manufacturing Strategies

Flexible batch sizes can optimize supply, but equipment and processing challenges are still being addressed.

Jennifer Markarian

The United States Food and Drug Administration (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 26 Feb. 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).

The concept of batch size is one of the concerns that some companies may have when considering whether to move to continuous manufacturing.

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).

Whether frequent changeovers can be performed efficiently to enable short duration runs and small batches is still an open question. 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).

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It is well known that particle characterization is an important consideration when ensuring optimal product development and efficient manufacturing within the pharma industry. Variance in particle properties can create handling challenges, and if manufacturers do not correctly characterize a powder and do not have a good understanding of powder behaviour, the ultimate outcome will more than likely be a poor-quality product.

Jamie Clayton, operations director at Freeman Technology, spoke to Pharmaceutical Technology Europe about the criticality of particle characterization, particularly when considering bulk powder behaviour, some important considerations for developers, and technologies available and in the pipeline.

Crucial for pharma development

PTE: 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 behaviour 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 behaviour. 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. Behaviour 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

PTE: 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 behavioural 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. Tabletting 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 difficult 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

“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

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

PTE: 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 behaviour. Performed using a powder rheometer, dynamic testing quantifies the energy associated with moving a powder under different stress and flow regimes. Powders can be analysed 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.

PTE: 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): For particle and powder properties that are routinely measured to support development and manufacture, there is a natural inclination towards real-time, in-line measurement. In-line technology eliminates any requirement for sampling, automatically measuring in situ under the most representative conditions and evaluating a much higher proportion of the process stream—all of which are crucial gains when working with powders. By providing more representative and relevant data, faster than at-line and off-line techniques, in-line technology has the potential to transform the ability to control and optimize pharmaceutical processes.

In-line technology is well-advanced in some areas but in others it is just emerging. For powder characterization, an important advance is the introduction of in-line drag force flow (DFF) technology. This provides continuous, real-time measurement of the local forces associated with the movement of powders or granules within a process. A DFF sensor is a fine needle-like structure that can be inserted directly into process equipment. The data generated have been shown to correlate with established off-line techniques, demonstrating the potential to transfer process and product-relevant specifications from the lab into the manufacturing line.

Dosage form nuances

PTE: Are there particular particle and bulk powder characteristics that developers should be mindful of when considering different dosage forms?

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 behaviour was found to be important (a measure of cohesion), but so too was the impact of interparticular 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.

In terms of tabletting, 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 behaviour 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**

**PTE:** 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.

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

—Jamie Clayton

**PTE:** 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.

**References**

5. USP, USP General Chapter <1174> “Powder Flow” (US Pharmacopreal Convention, Rockville, Maryland, USA, 2012).
Successful technology transfer is essential to enable biopharmaceutical clients to safeguard supply, improve distribution, and reduce programme 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 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 project progresses.
### Table I: Questions to ask when selecting a contract development and manufacturing organization (CDMO) to manage technology transfer of your product.

<table>
<thead>
<tr>
<th>Number</th>
<th>Question</th>
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<tbody>
<tr>
<td>1.</td>
<td>How can we develop trust and transparency early in the project?</td>
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<tr>
<td>2.</td>
<td>Have you demonstrated technical expertise and experience in delivering a variety of new products successfully?</td>
</tr>
<tr>
<td>3.</td>
<td>What opportunities do we have to leverage the strengths and knowledge from each other that can best benefit the team and project?</td>
</tr>
<tr>
<td>4.</td>
<td>What tools do you use to control the project timeline?</td>
</tr>
<tr>
<td>5.</td>
<td>How do you capture and mitigate risks?</td>
</tr>
<tr>
<td>6.</td>
<td>What is your communication and escalation process?</td>
</tr>
<tr>
<td>7.</td>
<td>How do you use the power of a network to meet customers’ needs?</td>
</tr>
<tr>
<td>8.</td>
<td>Where can we partner to identify process improvement opportunities?</td>
</tr>
<tr>
<td>9.</td>
<td>Do you have experience and expertise with intended technologies?</td>
</tr>
<tr>
<td>10.</td>
<td>Is there sufficient capacity to manage forecasted demand?</td>
</tr>
<tr>
<td>11.</td>
<td>Do you have a governance model to ensure the project remains on track?</td>
</tr>
<tr>
<td>12.</td>
<td>What functions make up the project team and what is their experience level?</td>
</tr>
<tr>
<td>13.</td>
<td>Is there flexibility to align on differences in requirements?</td>
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#### 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 programme 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 consider 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.

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
Operations

need to be mindful of a compound’s understanding of the process and should be used to ensure a robust principles of quality by design (QbD) transfer to be successful, the management toolkit, for a technology In addition to a robust project aid to technology transfer Quality by design as an knowledge and resources to manage global forum is key to leverage across the network. Similarly, this 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 programme 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 modelling

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 modelling 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...
Figure 4: Design of experiment conducted for ‘compound X’ to identify the critical process parameters and critical quality attributes as part of process optimization and scale-up.

Successful Technology Transfer

Pharmaceutical Technology Europe 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.

Best practices and challenges

PTE: 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 [contract development and manufacturing organization], 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 programme moves through each phase of its introduction and throughout life.

—Susan Haingey

To read this interview in its entirety, visit PharmTech.com.

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. PTE

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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. 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 complaints falls under regulatory scrutiny (4).

The first element of a robust complaint system is to establish a standard operating procedure (SOP) that indicates the communication vehicle used to collect customer complaint information such as use of a dedicated telephone number and/or an Internet link where customers can report the problem they are having with your product. 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 established, they need to be routinely monitored. The monitoring frequency should be established in the SOP. The phone line and the weblink 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 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 communication avenues and information requirements are established, determine the complaint categories, such as 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.

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.) 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. All complaints, however, are available for regulatory review during an inspection.

Establishing a robust and well-documented complaint handling process is an 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.

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2. FDA, 21 *CFR* 211.180 (e)(2), Current Good Manufacturing Practice for Finished Pharmaceuticals, Records and Reports, 1 April 2018.
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