Building Effective Quality Programmes

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Designing Specialty Dosage Forms

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Striking a Landmark Deal

After years of discussions around pricing, UK governmental bodies and Vertex have finally reached an agreement on cystic fibrosis treatments.

In recent news, it was announced that after several years of clashing over pricing, National Health Service (NHS) England and Vertex have finally struck a deal, which will give patients in England access to treatments for cystic fibrosis, Orkambi, Symkevi, and Kalydeco (1). The definitive agreement covers three medicines from Vertex that are licensed in the United Kingdom for the treatment of cystic fibrosis.

For cystic fibrosis sufferers in the UK, a country that has the second highest prevalence of cystic fibrosis in the world, it has been a four-year long wait to gain access to Vertex’s Orkambi treatment, which gained European approval in 2015 (2). Orkambi (lumacaftor/ivacaftor) is the first medicine to treat the underlying causes of cystic fibrosis (lumacaftor/ivacaftor) is the first medicine to treat the underlying causes of cystic fibrosis.

With Vertex and NHS England at an impasse, tensions were frayed and inflammatory remarks and bravado on both sides ensued. As campaigners persisted in their efforts to gain access to Vertex’s treatments, the UK government was called upon to break the deadlock on pricing, even with some calls for the government to invoke ‘Crown Use’, which would have enabled third parties to access intellectual property of Vertex for the creation of generic versions of the medicine, Orkambi (4).

The potential ramifications of Crown Use were not lost on Vertex, which announced its reaction in a statement, according to the BBC (5). “To invoke Crown Use and provide third parties access to Vertex’s intellectual property would seriously undermine our ability to achieve these goals and would significantly weaken incentives for future innovation,” the statement read.

The deal is struck
An agreement has now finally been achieved, however, and despite exact pricing for the treatment being unknown publically, it has been hypothesized that it is an amount ‘significantly less than the sum originally asked for’ (5). As a result of the agreement, an important and vast market has ultimately now been penetrated by Vertex, adding to markets in Spain, Australia, and Scotland.

“The UK has the second highest prevalence of cystic fibrosis of any country in the world, so today is an important and long hoped for moment for children and adults living with cystic fibrosis,” said Simon Stevens, NHS chief executive (1). “That fact also means that any drug company wanting to succeed commercially in this field needs to work constructively with the NHS. I’m pleased that Vertex has now agreed a deal that is good for our patients and fair to British taxpayers.”

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2. Vertex, “Vertex Receives EU Approval for Orkambi (lumacaftor/ivacaftor), the First Medicine to Treat the Underlying Cause of Cystic Fibrosis in People Ages 12 and Older with Two Copies of the F508del Mutation,” vrtx.com, Press Release, 20 Nov. 2015.

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**Editor’s Comment**

**Striking a Landmark Deal**

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Charles Ross & Son Company
www.mixers.com

Innomech Benchtop Systems

The new Innomech Benchtop Systems developed for and offered by Aston Particle Technologies (APT) combine two benchtop systems to organize small amounts of blended pharmaceutical powders for use in APT’s formulation development projects.

The system uses the company’s one-step particle engineering technology to prepare up to 10 grams of blended material while maintaining the same process technology, conditions, and recipe-based control system of APT’s two-kilogram pilot-scale production unit. Through its ability to produce small quantities for proof of principle studies, pharmaceutical companies have the option to buy in bulk quantities or to scale up its synthesis of specific ingredients.

Aston Particle Technologies
www.astonparticletechnologies.com

Powder Dosing Unit

Extruder by MG America is a new powder dosing unit that only requires one dosing disk per capsule size, regardless of the dosage. The device was designed to work in conjunction with the company’s AlternA70N Intermittent Motion Capsule Filler, which is used for dosing and filling powders and pellets into hard-shell gelatin capsules.

The new unit comes equipped with a redesigned dosing container and disk to simplify the capsule filling process and improve dosing accuracy and weight consistency. It also reduces product wastage by maintaining the powder inside the container and disk to control powder loss, improve yields, and cut down on cleanup time.

MG America
www.mgamerica.com

Automated Cotton Inserter

Deitz Company introduced the Pharmafill™ CS2 to its line of automated cotton inserters. The new device comes with a higher speed configuration that increases its filling rate to 90 inserts per minute compared to its standard configuration of 80 inserts per minute, a 12.5% increase.

The updated inserter separates cotton, rayon, and polyester from a continuous coil into individual pieces that are then inserted through three-inch long tubes that can accommodate cotton pieces from 2.0–5.5 inches in length, which then release the pieces downstream while preparing to fill the next bottle. The device is computer-controlled, delivers 99.99% insertion accuracy, and automatically stops the process if the cotton roll is ready for replacement or if no bottle is present.

Deitz Company
www.Deitzco.com
Investigating NDMA Impurities at EMA’s Request

Companies are facing a huge undertaking to be able to complete risk evaluations of all medicines containing chemically synthesized APIs by March 2020.

The European Medicines Agency (EMA) and the European Union’s national licensing authorities have taken the unusual step of requesting that pharma companies investigate the production processes for all medicines containing chemically synthesized active substances for the possible presence of nitrosamines, which are classified as probable human carcinogens (1). Many pharma companies, therefore, face a massive task of completing risk evaluations of their production processes and suppliers, including producers of starting materials, by March 2020.

The EU measures follow an EMA recommendation in January 2019 that companies making sartan blood pressure medicines—also known as angiotensin II receptor blockers—reassess their production processes to avoid the creation of nitrosamine impurities (2). This action was preceded by the discovery in mid-2018 that Zhejiang Huahai, a Chinese drug manufacturer, was making a sartan medicine, valsartan, which contained nitrosamine impurities (2). Soon afterwards, nitrosamines—mainly N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA)—were detected in four other sartan medicines (2).

The impurities were found to be formed in certain conditions during the production of sartans containing a specific ring structure—known as a tetrazole ring—and when particular solvents, reagents, and other raw materials were used. Also, some sartans could contain impurities because their manufacturers had inadvertently used contaminated equipment or reagents.

Regulatory actions

After its review of sartans, completed in January 2019, EMA set a two to three-year transition period for marketing-authorization holders (MAHs) with nitrosamines in their sartan medicines to make changes in their processes during which they would have to adhere to strict limits on the levels of the impurities. After the two years, MAHs would be required to demonstrate that their sartan products had no quantifiable levels of nitrosamines before they could be marketed in the EU.

Furthermore, the agency warned that there was a potential for nitrosamines to be present in APIs of other non-sartan medicines. Then, in April 2019, EMA revealed that both itself and national authorities were requesting ‘as a precaution’ that companies using certain reagents to manufacture the diabetes medicine pioglitazone test their products and check their processes to rule out the presence of NDMA (2).

The request followed the detection of low levels of NDMA in a few batches of pioglitazone made by Hetero Labs in India (2). The levels were within strict safe limits previously set for sartans by guidelines of the Geneva-based International Council for Harmonization (ICH).

In September 2019, EMA announced it is to start a review of prescription and over-the-counter versions of ranitidine, a histamine-2 blocker for the treatment of excess acid in the stomach causing conditions like heartburn and ulcers. This notice came after tests showed that some ranitidine products contained NDMA. At the same time, the agency disclosed that its Committee for Medicinal Products for Human Use (CHMP) would be providing guidance on avoiding the presence of nitrosamines in human medicines containing chemically synthesized active substances (3). “It is of paramount importance that we learn from our experience with sartans and take a proactive approach for other classes of medicines,” said Guido Rasi, EMA’s executive director (3).

Initially CHMP will be basing its guidance on an investigation of processes for making chemically synthesized medicines and their active ingredients. But in a two-part procedure, CHMP will also be considering whether its study should be extended to other forms of medicines, especially biopharmaceuticals (3). CHMP’s examination will cover the whole value chain from starting materials through to finished products.

The task will be almost unprecedented in its scale for the EU medicine authorities, who will have to rely on MAHs collecting information throughout their chains. This will be made more difficult by the practice among a lot of MAHs of relying on the contracting out of production at each stage of the chain.

“There were very few cases in the past where carcinogenic impurities or contaminations were found in authorized medicines,” an EMA spokesperson told Pharmaceutical Technology Europe. “However, these [cases] were very specific to one product or a manufacturing issue.”
Following EU directives

The EU actions on sartans, pioglitazone, and ranitidine are being performed under a 2001 EU directive and its subsequent amendments on a quality and safety code for pharmaceuticals for transposition into member states’ legislation (4). These actions are mainly being done under the directive’s article 31 as well as 107 on urgent procedures under which the supply of specific medicines may be prohibited (4).

However, the 2001 directive and its amendments are related to the quality, safety, and efficacy of individual drugs or groups of types of medicines (4). The articles within the directive also allow EU regulatory authorities to impose mandatory requirements on companies.

The review of ranitidine medicines, for example, will be performed by CHMP under article 31 of the directive. The review’s conclusion will be passed to the European Commission for the possible creation of binding decisions applicable in all EU member states.

The broad sweep of EMA’s CHMP guidance being drawn up on the prevention of nitrosamine impurities has had to be made under different legislation—a 2004 regulation laying down EU procedures for the authorization and supervision of medicines (5). The guidance is being prepared under article 5 (3) of the regulation, which allows CHMP to provide an opinion on any scientific matter concerning medicines evaluation. But it is unclear whether the opinion can be used as a basis for binding regulatory measures.

EMA sent out a notice to companies on 19 September 2019 requesting that, as a result of the article 31 review of sartans, pioglitazone, and ranitidine, pharma companies evaluate the risk of nitrosamine presence in chemically synthesized medicines (1). Under the 2001 directive, the notice pointed out that MAHs are responsible for the quality, safety, and efficacy of their products, including the quality of the APIs, excipients, and raw materials (1).

Challenging requirements

API manufacturers and others in the supply chain are obliged to make the information necessary for risk evaluations available to MAHs and for taking responsibility for the quality of the finished product and its active substance, as per the notice. This requirement may cause problems for manufacturers of products with active substance master files (ASMFs) and certification suitability to the monographs of the European Pharmacopoeia (CEPs) because these contain information not available to MAHs (1). But the notice implies that it may suffice for MAHs to ensure that “robust risk evaluations have been appropriately carried out by the ASMF or CEP holder.”

In the notice, EMA provides more information—since its sartans review in January 2019—about potential sources of nitrosamine impurities about which, until mid-2018, there was not much awareness among many pharmaceuticals manufacturers (1). The use of sodium or other nitrites in the presence of secondary or tertiary amines is a major cause of nitrosamine formation, the notice specified. Secondary amines can be present in reagents and solvents as impurities or degradants of reagents, solvents, and APIs. Amide solvents, for example, can degrade to secondary amines. Tertiary amines are also common functional groups in APIs and their precursors.

There have been cases where sodium nitrite has been used as a reagent in one step and then carried over into subsequent steps, where, despite extensive purification, it has reacted against an amine to generate a nitrosamine impurity, according to the notice.

Recycled solvents, reagents, and catalysts may pose a risk of nitrosamine formation due to the presence of amines in waste streams. Third parties, to which recovery of materials, such as solvents and reagents, are frequently outsourced, can use non-dedicated equipment potentially leading to cross-contamination. Starting materials contaminated with impurities like nitrites are another source of nitrosamines, the notice warned.

Prioritizing products

“In view of the large number of authorized products (to be evaluated), MAHs are requested to prioritize products following a risk-based approach,” the EMA spokesperson told Pharmaceutical Technology Europe. “For the purposes of this prioritization, MAHs may consider factors such as the maximum daily dose taken, duration of treatment, therapeutic indication, and number of patients treated.”

“MAHs and manufacturers should test a representative number of samples of the relevant starting material, intermediate, API, or finished product, with the number of batches/samples tested (being) scientifically justified,” the spokesperson added.

Companies with nitrosamine problems in their production processes and supply chains will have six months to complete a risk evaluation. Then a maximum of three years to perform a confirmatory test on an identified risk of nitrosamine presence. Finally, if they have to change a production process, they will have to gain authorization of a variation. It could all be a long procedure.

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2. EC, “Angiotensin-II-Receptor Antagonists (Sartans) Containing a Tetrazole Group,” Review (final decision), EMA 248364/2019 Rev. 1 (Amsterdam, 1 February 2019)
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Building Effective Quality Programmes

An effective quality control unit is independent from manufacturing and ensures current standards are followed.

Susan Haigney

The safety and efficacy of pharmaceutical products is of utmost importance. Regulations in the United States require that pharmaceutical companies establish a quality control unit to perform quality functions to ensure their products meet specifications and are safe for use. This unit also has the task of assuring regulators that good manufacturing practices (GMPs) are being followed. Regulators in Europe and other parts of the world have similar but varied requirements.

The consequences of failing to ensure the quality of drug products range from the most egregious—adverse effects on patients—to potential regulatory actions, such as consent decrees, import bans, and seizure of product. Regulatory responses can include reports such as US Food and Drug Administration (FDA) Form 483 observations, inspection findings from the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom, or requests for urgent actions such as FDA warning letters. In addition to regulatory actions, an ineffective quality system may also affect a pharmaceutical company’s success. “Ultimately the consequences are reduced profitability, as scrap, rework, and downtime are increased,” says Karen Ginsbury, CEO of PCI Pharmaceutical Consulting Israel Ltd.

Several warning letters issued by FDA to various pharmaceutical companies located in the US and around the world in 2019, however, seem to have a common theme: a lack of a properly functioning quality control (QC) unit (1–4). The agency has cited companies for everything from failure to establish an adequate QC unit to QC units not performing their duties properly.

“Many FDA 483 observations have been issued for quality units failing to fulfil all their responsibilities. If a firm releases product (or other material) in the absence of a quality unit, this is even more egregious,” says Mary Oates, vice-president Compliance Services, at Lachman Consultant Services, Inc. “There may also be consequences for patients. If there is no quality unit, in all probability there will be significant gaps in the pharmaceutical quality system, potentially presenting risk to patients if processes and controls are not in place to ensure product quality.”

Pharmaceutical companies are responsible for ensuring the standards of all drug components, including excipients, APIs, and packaging materials, says Susan J. Schniepp, executive vice-president of post-approval pharma and distinguished fellow at Regulatory Compliance Associates, and it is the QC unit’s responsibility to investigate why any of these components fails to meet those standards.

“The quality control unit plays a huge part in making sure that products meet the proper applicable standards before they are released,” says Schniepp. “It’s interesting to note that the quality control unit is the only functional unit required by law. This is
not to imply that the quality unit works in a vacuum, but rather that it facilitates the investigation into any failures. The QC unit has the sole responsibility of releasing product. No other department in an organization has this authority, and it cannot be delegated. Bottom line, we rely on the quality unit to make sure that product released to the market is safe and effective.”

With quality being so imperative, how is it that pharmaceutical companies are improperly maintaining such a vital part of their operations? One could argue that a failure to create a quality culture in the organization from the top to bottom may be a cause for this failure. The following discusses why companies may be faltering in this area and what a company can do to maintain a more effective quality control unit.

What is a quality control unit?
One of the challenges in ensuring quality may be the varied regulations and requirements pharmaceutical companies are required to follow. When it comes to the QC unit, there seems to be some confusion and debate about what exactly a QC unit is and what duties it performs. This confusion can be somewhat blamed on different names for the quality department itself and the language in the US and EU regulations.

According to Ginsbury, the message in the GMP regulations is unclear and possibly misleading. “Based on the definitions in the GMPs, we can conclude that in the United States and the European Union, the QC unit apparently has a rather narrow role, limited to sampling, testing, and making judgements as to product quality (or lack thereof, i.e., release/reject). This is not necessarily, nor ever was, the intent of the regulator,” insists Ginsbury. The GMP regulations are more product than process focused, says Ginsbury, “which can result in executives mistakenly believing that product meeting all release specifications may be released even when there are serious GMP deviations related to the batch or other batches of product, or equipment or facility.”

“Under QC unit roles, there is not much to be found at all about establishing, maintaining, and continuously improving the quality system, measuring (quality metrics), and reporting to management as to how well the system is doing. The QC unit is perceived as a sort of judge, who with unusual wisdom can ‘decide’ if faulty/flawed product produced with a deviation or non-conformity is ‘impacted’ or not impacted by the non-conformity. The concept of zero defects and prevention of defects, which is the basis for any true quality system, and the Plan-Do-Check-Act process-based cycle are absent (in the written GMP regulations),” says Ginsbury.

Russell Madsen, president of The Williamsburg Group, LLC, argues that, in the US, the QC unit has “sweeping responsibilities specified in 21 Code of Federal Regulations (CFR) §211.22, including ‘the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product’” (5).

So, what is a QC unit? US 21 CFR 210.3(15) defines the quality control unit as “any person or organizational element designated by the firm to be responsible for the duties relating to quality control” (6).

According to Oates, the QC unit includes both quality assurance and quality control functions and should be involved in the approval of the drug product, testing results, production records, procedures, and all materials that might affect the final drug product whether that product is produced in house or “manufactured, processed, packed, or held under contract by another company,” says Oates.

Simply, the QC unit includes and oversees both quality assurance (QA) and QC. Both Schniepp and Ginsbury state it is important to understand the difference between QA and QC. Ginsbury further states that neither of these on their own are what the regulator intended regarding the QC unit. “The quality unit should be [...] preventing defects and non-conformities from happening by planning (including proactive risk assessment/management during design of processes, checking

[validation]), monitoring, and continuous improvement,” says Ginsbury. “This needs to be real time and not as current Product Quality Reviews are performed—annually with a lag of up to 18 months from when the data [were] collected.”

The QC unit should be independent from manufacturing and should serve as oversight for the overall quality system and set the quality culture within the company. “The [QC] unit can be seen to have two tasks: quality testing and the decision to pass or fail on the basis of the results. These two functions are usually separated into a quality control laboratory (testing) and quality assurance (release and documents administration). There is a good reason for this because it takes the release decision away from the testing group and keeps it independent,” says Chris Moreton, PhD, partner at FinnBrit Consulting. Oates agrees, “The quality unit itself manufactures nothing. It is responsible for oversight.”

This independence contributes to overall product quality, says Oates, especially when it comes to quality decisions and the commitment to delivering quality products. “All firms in the pharmaceutical industry, no matter the size, must have robust processes and systems to enable right-first-time manufacturing (inclusive of all GMP activities along the supply chain) and, perhaps most critically, a culture that puts the interests of patients first. Only then will product quality be assured,” says Oates.

In Europe, the batch release/reject decision falls to the role of a Qualified Person (QP) as defined in the European guidelines (7, 8). Europe Directive 2001/83/EC (9) states, “Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 48, without prejudice to his relationship with the holder of the manufacturing authorization, is responsible, in the context of the procedures referred to in Article 52, for securing: (a) in the case of medicinal products manufactured within the Member States concerned, that each batch of medicinal products has been manufactured and checked in compliance with the laws in
force in that Member State and in accordance with the requirements of the marketing authorization....”

**Setting up a quality control unit**

An understanding of the role of the QC unit is the first step in creating and maintaining the QC unit. A company’s standard operating procedures (SOPs) must clearly define the role of the QC unit, says Oates. Processes that are clear and easy to follow in repetition should be implemented, agrees Bo Henry, director of Quality Control at Catalent. Documentation should be standardized, and staff should be trained to ensure the integrity of data. “Finally, build a culture focused on the patient. With an effective training programme and a culture of quality, the entire organization will be able to approach decision making effectively,” says Henry.

The makeup of the unit is the next important step. The QC unit should be comprised of personnel with knowledge of the products and processes they oversee, says Madsen, and should be familiar with the GMP regulations. Oates agrees, “They must understand the processes and systems for which they have oversight. For example, an employee in QA responsible for oversight of aseptic media fills must fully understand the critical aspects of aseptic manufacturing, grasping the ‘why’ as well as the ‘what.’ Ideally, a quality control unit would include some employees who have prior experience in manufacturing. This deeper understanding of the production processes and systems enhances their ability to provide appropriate oversight,” says Oates. According to Ginsbury, in Europe, these requirements are stated in the EU GMP guidelines (10).

According to Mark TePaske, PhD, senior director, Global Regulatory Affairs, Quality and Compliance at Cambrex, the nature of pharmaceutical products requires more stringent controls than other industries. QC personnel operate complex analytical instruments and must follow approved written procedures, says TePaske. “QC needs metrology resources (often contractors) to qualify and maintain instruments; analysts to set-up and operate instruments and perform tests methods; persons to qualify/validate test methods; technically competent persons to draft procedures; personnel to perform peer review of data and supervisors (as required by the FDA OOS guidance document [11]), support investigations and troubleshoot; and persons to approve and report results. All personnel need to be suitably trained by qualified trainers with training documented. This list assumes that QC relies on [the quality assurance department] for document control, issuance, and retention,” says TePaske.

A QC unit should consist of personnel from quality assurance, quality control, validation, and sterility assurance departments, according to Henry. It may also include personnel from document management and quality engineering. All personnel must understand how their role ultimately affects patients, says Henry. “It is also critical to align with all applicable regulations and guidance for the product. Start by creating a quality manual, then build foundational standard operating procedures. Performing an initial process map of the quality and operational processes prior to generating quality management system policies and procedures is a very useful exercise,” says Henry.

**Best practices for quality control units**

The key aspects of an effective QC unit include well-written SOPs, well-informed personnel, and a clear understanding of roles and responsibilities of everyone involved. The development of a quality culture throughout the organization is also important. Ginsbury stresses that developing this quality culture is only possible if executive management is brought on board.

To ensure continued quality and uninterrupted supply of pharmaceutical products that are distributed to patients, the QC unit must stay apprised with changing GMPs, says Oates. Procedures that at one point were compliant with the regulations may no longer be. “This is often seen in the areas of validation and aseptic manufacturing. Regulatory expectations are increasing, and some firms are not remaining current,” says Oates.

Written procedures must be developed and followed according to the regulations. These procedures should be thorough and complete, says Oates. “For example, validation for a manufacturing process may not have been completed or the responsibilities of the quality unit may not be defined in a procedure.” Procedures that lack sufficient detail can lead to quality problems, says TePaske. “The most common problems here are that some procedures lack enough detail to ensure control, other procedures omit required information (e.g., the FDA out-of-specification guidance document includes an extensive list of considerations), and some procedures contain too many or contradictory details and are impossible to accurately follow.”

Each individual’s role within the QC unit and the organization must also be clearly defined, says Henry. “The plan should outline which individuals need to be informed of a deviation, and who can make the decision on next steps if the next steps are not captured already in the procedure. As an organization grows, it can become difficult to maintain clarity on written procedures as more people are trained and asked to execute the procedure with a reproducible result. It is extremely important to revisit the procedure at an established frequency to revise it as needed for clarity.”

Failure to develop and follow such procedures may lead to regulatory actions. “When a firm receives a finding regarding the quality unit, it must look more holistically at its controls than perhaps is evident from the observation itself,” says Oates. There is also the problem of a “misalignment” of practices and written procedures, according to Oates. “Operators may execute a manufacturing process in one way while the SOP indicates it should be done differently. Additionally, it is possible that the validation document may not be aligned with either the actual or written practice,” says Oates.
Ensuring that deviations are properly investigated is also imperative for the QC unit. Oates stresses that it is the QC unit’s responsibility to define what constitutes a deviation and that this definition must be clearly communicated to the rest of the organization. “Training with examples must be provided so that the understanding of what is a deviation is fully calibrated across the organization,” says Oates.

The QC unit must have a system of “escalating” the investigation and resolution of deviations. Root cause must be identified and corrective actions and preventive actions (CAPAs) should be established. Henry states that investigations should remove human performance from the equation. “Most importantly, the product strength, identity, safety, purity, and quality should be considered when determining the impact of the deviation and ultimately the overall integrity of the batch by the quality control unit.”

“Firms can fall into a trap of being more focused on product release than on completing a holistic investigation, and the quality unit has the obligation to ensure the investigation is complete and appropriately supports any decisions being taken,” says Oates. Any trends found across multiple investigations should also have CAPAs implemented, and the QC unit should look for common themes. “Continuous improvement must be an objective of the quality unit and the firm as a whole,” says Oates. “Attention must also be given as to whether regulatory notification is required in a prescribed timeframe.”

“Top management and the QC unit must work in harmony to ensure there are adequate resources to investigate and correct situations that result in deviations. The importance of finding and correcting root causes cannot be overemphasized, so that deviations do not recur and overwhelm the organization,” stresses Madsen.

Establishing a quality culture throughout the organization is an important way to ensure that these steps are being taken. “It all comes down to training and motivation. Everybody, from the most junior to the most senior members of the organization, should be thinking ‘Quality’. This [quality culture] is obviously important in manufacturing and quality groups, but it is also important in finance, marketing, sales, etc. For example, there are always pressures to contain costs, but this should not be to the extent that people tend to gloss over things because there is not time or resources to deal with it properly. There are pressures to get the medicinal products into the supply chain as quickly and efficiently as possible, but this should not compromise patient safety,” says Moreton.

Conclusion
An effective QC unit must be independent of the manufacturing unit, says Oates, and the QC unit’s final decision on the release of product must be respected. “It is never appropriate to pressure the quality unit to release product to meet business needs if the product is not acceptable for release,” says Oates. “The quality unit must have a single, final decision-maker who is ultimately responsible for quality decisions.”

Pharma company executives should be aware that the quality of their products is a responsibility of many components of the organization and not the sole responsibility of the QC unit. “Perhaps the biggest mistake is for the firm to assume that the quality unit is responsible for quality. Manufacturing is responsible for product quality. The quality unit provides the framework in which GMP activities occur and subsequent, ongoing oversight and support for continuous improvement,” says Oates.

Ultimately, a successful quality control system requires a dedication to quality and investigating problems. “Small issues have a way of snowballing. Additionally, quality units cannot ensure product quality. Product quality can only be ensured when all company organizational units work in harmony, with product quality and patient safety as their primary goals,” says Madsen.

References
5. 21 CFR §211.22
Adapting APIs for Specialty Dosage Forms

Several factors must be considered when reformulating APIs for paediatric, geriatric, and other specialty patient populations.

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

Increasing emphasis on patient centricity is driving the development of different oral dosage forms of APIs used in adult products for specialty patient populations. Poor patient compliance is a significant issue in the pharmaceutical industry that can be addressed to a significant degree through the formulation of dosage forms designed for convenience and ease of use.

Modification of adult medications for children by dividing tablets or capsules into smaller segments to achieve lower doses or aid in swallowing; however, can lead to incorrect and/or nonuniform doses and compromise the performance of any sustained-release coating in the product. In some cases, excipients suitable for adult formulations can pose safety issues for children.

Age-appropriate medications are now required by regulatory agencies for children. Elderly patients and patients suffering from dementia and disorders that lead to problems with swallowing also benefit from specialty dosage forms. In all of these cases, the emphasis is placed on patient acceptability, which can be impacted by physiological, physical, and psychological factors.

**Determining acceptability**

“Overall, the practicality of administering an existing drug to a different patient population will determine its acceptability,” says Rob Harris, director, science and technology at Catalent.

Specifically, there are several factors to consider. The first, according to Jim Jingjun Huang, founder and CEO of Ascendia Pharmaceuticals, is efficacy and safety, which is determined by extrapolating the pharmacokinetics (PK) and pharmacodynamics (PD) for the existing formulation to the targeted population. The acceptability of the excipients in the existing formulation in the target population—taking their use levels into consideration—must also be established. For many specialty populations, the swallowability and taste of the existing formulation may need to be modified. Finally, dose accuracy, and if appropriate flexibility, must also be assured for the target population.

“Taste-masking, swallowability, dose flexibility, and excipient acceptability are all important for paediatric formulations, whereas dosing accuracy, swallowability, and the capability for multi-drug administration are important for geriatric formulations,” Huang notes.

For instance, Harris points to tablets, which are suitable for teenagers, but not patients two years old or younger. The paediatric patient group is unique, adds Anthony Qu, vice-president of scientific affairs for Cambrex. “The paediatric patient population includes infants, children, and adolescents. You cannot simply cut an adult dosage down. Paediatric formulations should vary from adult formulations depending on the patient age, body size, swallowing capability, and PK and PD profiles,” he asserts.

It is also important to note, according to Qu, that paediatric formulations can benefit other patient groups that have swallowing issues, such as the elderly, patients who have had a stroke, or patients with long-term diseases such as Parkinson’s or Alzheimer’s.

There are many sources of information to assess patient acceptability. “The fastest and least costly method of evaluation is to review relevant publications, the content of which include results of patient focus groups or patient and caregiver surveys,” Harris says.

**Challenges to reformulation**

There are numerous challenges to reformulating existing adult products for specialty patient populations. For all of these types of projects, accurate extrapolation of the PK/PD can present real difficulties, according to Huang.

For most specialty populations, swallowability and palatability are key elements in the design of suitable dosage forms. “Most drugs have an
unpleasant taste, and, therefore, due consideration needs to be given to making medicines acceptable from this perspective,” observes Harris. For children and the elderly, the actual dose can also be problematic; while an adult may be able to take a large tablet containing 500 mg of drug, administering a similar-sized tablet to a five-year-old child is much more challenging, he notes.

The physical differences of age, body weight, swallowing capability, and tolerance within the paediatric population are also challenging and create the need for dose flexibility, according to Qu. He adds that stability, shelf-life, and bioavailability issues can further complicate formulation development. Ensuring excipient acceptability for paediatric formulations adds another layer of complexity, according to Huang.

**First steps in reformulation**

The first step in a reformulation project for a specialty population is to consider the age range of the patients and the dose range of the drug to be given. It is then important, observes Harris, to consider the drivers for achieving dose acceptability and compliance for that patient population, and what might the complications be in administering the drug to these patients.

Questions that should be answered when looking to overcome reformulation challenges, according to Qu, are:

- What measurable dose form is required based on mg/kg body weight?
- Does the API formulation have a bad taste, and if so, can this taste be suppressed or masked?
- Is the API soluble or not soluble?
- Is the formulation stable or not stable?

“The goal is to determine the formulation strategy that will ensure similar exposure of the API in the new dosage form for the new patient population as is achieved with the adult product and address the specific needs of the target population,” Huang explains. The solubility of the API must be considered to determine if a solubilization technology will be needed to achieve this goal. The stability of the API will determine whether a liquid (i.e., solution, syrup, suspension) product is possible, or if a solid dosage form will be necessary, Qu adds.

**Many potential solutions**

Once the various factors have been considered and the relevant questions answered, it is possible to determine the optimum formulation and oral dosage approach. The main options include traditional liquid and solid (i.e., tablets, capsules) formulations, as well as newer dosage forms, such as chewable and fast dissolving tablets, rapidly dissolving and mucoadhesive oral thin films and multi-particulate formulations such as mini-tablets.

“The traditional approach has been to use solution or suspension formulations because they are easy to swallow and provide dose flexibility.
However, the use of sugars, flavours, and preservatives in these formulations can have detrimental effects on children and are consequently becoming less popular,” says Harris. These formulations also typically need to be refrigerated in-between use, have a shorter shelf-life, and can have overall stability issues compared to other forms, according to Harris. Furthermore, accurate dosing can be an issue due to varying spoon sizes.

Traditional solid-dosage forms are well-established technologies that have stable, long-term shelf-lives, are pre-measured for dosing, and can be coated to mask taste or added to food, according to Qu. “Conversely,” he says, “they can be difficult to swallow for some patients, and certain types of formulations are hydroscopic and require special packaging and storage in a dry place.”

Chewable tablets are another option for paediatric patients. “These formulations typically benefit from enhanced bioavailability and are convenient because water is not required for consumption and absorption is typically fast,” Qu says. However, these formulations typically contain sorbitol, which could have potential side effects in children. Other factors, according to Qu, are the material flow, types of lubricants used, disintegration acceptance, taste, compressibility, and stability.

Orally dispersible tablets in which the tablet rapidly disintegrates in the mouth have become popular and certainly allow for easy swallowing of the dose, according to Harris. Qu notes, however, that they present their own hurdles as well, such as lower strength levels and half-lives.

Mini-tablets are the most common type of multi-particulate formulation. These small (typically 2–3 mm in diameter) versions of normal tablets can be readily swallowed by very young children. They also offer great dose flexibility, because the number of minitabs can be varied to achieve the required dose, according to Harris. In addition, unpleasant tastes can be masked using barrier coatings.

A further benefit of mini-tablets is the ability to combine different types of tablets in one dosage form (within a capsule or compressed into a tablet), according to Qu. “It is relatively easy to combine immediate and sustained release mini-tablets in one product. Similarly, mini-tablets facilitate the formulation of fixed-dose combination products containing two or three different APIs,” he observes.

One potential solution to the potential solubility, stability, and taste-masking issues is to utilize nanotechnologies, such as nanoparticles or nanoemulsions, which can encapsulate the molecules into a nano-formulation that can mask the taste and protect the compound from degradation, according to Huang.

Another approach, he says, could be a change in the route of administration to injectables; a long-acting injectable for chronic disease would address the taste, dose accuracy, safety, and compliance issues associated with oral dosage forms.

The excipient factor

For paediatric formulations, it is essential to ensure that all of the selected excipients are safe for consumption by children. “Excipients play a key role in how a drug product is manufactured, stored, consumed, and delivered in the body. Just like with dosage and formulation, not all excipients that are appropriate for adult formulations will work in paediatric formulations. Children may not be able to metabolize or eliminate the excipient in the same way that an adult can, which can cause issues such as stomach upset (indigestion, flatulence, diarrhea), breathing trouble, intoxication, or worse,” Qu explains.

In some cases, there may be different safety limits for an excipient that is used in an adult formulation versus a paediatric formulation, and guidance exists on this topic. In other cases, an excipient may need to be replaced completely with a different alternative. Formulators must decide what function each excipient is serving in the adult formulation, and then select and assess alternative, child-acceptable excipients that offer similar functionality, according to Harris. He points to the European Paediatric Formulation Initiative Safety and Toxicity of Excipients for Paediatrics database (1) as a good place to start in selecting suitable excipients for use in children-friendly medicines.

“Selecting suitable excipients for a paediatric formulation is not normally challenging, but there are restrictions. The key point here,” Harris stresses, “is that excipients are not inactive ingredients.”

Keys to success

Successful reformulation of adult medicines for specialty patient populations can be successfully achieved by starting with a ‘patient-first’ mind set, which requires consideration of the formulation type that will best suit the needs of the patient, not only for getting the drug into the body, but also for ease of use and patient acceptance, according to Harris.

The development of paediatric and other specialty formulations requires extensive knowledge and expertise in not only a variety of dosage forms and technologies, but awareness of the key determinants for patient acceptability. “As a result, many companies rely on experienced [contract development and manufacturing organizations] CDMOs with specialist expertise in this field,” says Qu. “Such CDMOs will be able to provide guidance and develop the right formulations that consider the age and taste preferences of the target population in the context of different dosage forms, in addition to paying attention to regulatory approval early in the development process,” he concludes.

Reference

Palatability is crucial for adherence and compliance to oral drug regimens.  

Avoiding bad or bitter tasting finished drug products is widely accepted as a way of improving patient adherence and compliance to a therapeutic regimen, particularly when considering pediatric and geriatric populations. Many APIs in development, however, are classified as bitter compounds.

Elaborating on this point, Krizia M. Karry, global technical marketing manager, BASF Pharma Solutions, highlights a study by Dagan-Wiener et al. which revealed that two-thirds of current clinical and experimental drugs were classified as bitter (1). “Aversion to bitterness, or in general, product palatability, has been demonstrated to affect treatment completion,” she says. “For example, in 2007 the average treatment completion rate of pediatric patients was only 58% with palatability and formulation being attributed as major contributing factors. To this day, this has not changed.”

In agreement, David Tisi, director of operations, Senopsys, adds that on top of bitterness, many active ingredients have other undesirable sensory attributes, such as smell or trigeminal irritation. “Furthermore, excipients used to increase drug solubility or used for preservation are known to create or exacerbate the taste-masking challenge,” he notes.

Understanding the challenges  

Going back 40 years, O’Mahony et al. performed a series of experiments assessing taste the perception of bitter or sour (2). In the experiments, it was realized that confusion between sour and bitter tastes existed in the general population. For Tisi, the difficulties in determining how a patient perceives the taste of an ingredient is a major challenge that must be overcome by the formulator. “Untrained healthy volunteers often describe drugs as ‘bad’ or ‘yucky’ tasting, which is not very helpful as there’s no ‘good’ or ‘yummy’ ingredient on the shelf to improve palatability,” he says.

From data compiled by Senopsys, taken from 101 taste assessment studies, it was found that the primary challenge in taste-masking was bitterness at 75%, followed by aromatics (10%), and trigeminal irritancy (8%). In APIs that were fundamentally tasteless, challenges were driven by excipient attributes (3).

“The reason these data are critically important is that the formulation strategies for mitigating bitterness, malodor, irritation, and texture are fundamentally different,” explains Tisi. “As these approaches differ, it’s important to correctly identify the aversive attributes at the outset.”

Predicting whether new compounds will be bitter or not is one of the biggest challenges, according to Karry. “Albeit unknown to most, there is not a clear understanding as to which chemical bonds, functional groups and compounds activate the bitter receptors in the tongue,” she says. “BitterDB, a database with more than 1000 bitter compounds, is available to formulators (4). Machine learning algorithms trained with these molecules are now used to predict bitterness of new compounds. This tool enables formulators to proactively think about methods to suppress bitterness and include in excipients meant for taste-masking.”

However, limiting drug release in the mouth brings about other challenges. The most effective taste-masking polymers are insoluble at pH > 5 but will immediately dissolve in stomach acids, explains Karry. “A consideration with using such excipients is that the formulation should allow for complete polymer solubilization in the stomach even with shorter gastric residence times (1 hr) or when the patient is in...
“Special attention should be given to tablets based on multiple-unit pellet systems (MUPS) which show faster gastric emptying times due to their small size and larger surface area. For these, the pellet diameter and coating weight gain need to be optimized with respect to polymer solubilization and drug release rate.”

Understanding the magnitude of taste-masking challenges is of great importance to Tisi who specifies that although in some instances it may be possible to overcome taste issues with a traditional excipient approach (such as sweeteners, buffers, or flavours) for other ingredients it may be necessary to ‘sequester’ them from the taste receptors to achieve palatability. “Information about the magnitude of the challenge at hand will allow the formulator to prioritize or eliminate certain dosage forms (e.g., the most difficult taste-masking challenges may not be suitable for a ready-to-use oral solution),” he stresses.

**Considering the patient population**
Specific patient populations, such as paediatrics and geriatrics, require more complicated taste-masking approaches. “For these patients, palatable oral formulations are required for acceptable dosing compliance,” comments Tisi. “In recognition, regulations in the United States and European Union are stimulating research into the development of drug products specifically labelled for paediatric dosing.”

Regulatory requirements and guidance are present in both the US and EU to help companies develop age-appropriate dosage forms for patients. Examples include the Paediatric Research Equity Act (PREA) in the US (5), and the Paediatric Regulation from EMA (6). These requirements typically lead to alternative dosage forms due to difficulties that are encountered by young children in swallowing traditional solid oral dosage forms, confirms Tisi. “However,” he continues, “children are not the only ones who suffer from difficulty of swallowing, a condition known as dysphagia. In the US, dysphagia affects 1 in 25 adults annually, not including patients with certain neurological and degenerative disorders (7). Accordingly, swallowability and palatability are important determinants of dosing compliance for all ages and conditions.”

Dose and tablet size are important considerations in addition to palatability when designing products for both paediatric and geriatric patient groups, adds Karry. “Parents prefer smaller tablets for their children but minitablets may be difficult to handle by geriatric patients,” she says. “To satisfy both requirements

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**Table I: General taste-masking approaches currently available and the specific limitations relating to each.**

<table>
<thead>
<tr>
<th>Approach</th>
<th>Mechanism</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signal interruption</strong></td>
<td>The use of an antagonist to inhibit taste—ligand binding</td>
<td>• Antagonist must follow same receptor pathway as API</td>
</tr>
<tr>
<td></td>
<td>• GPCR signal cascade blockers</td>
<td>• Functions best when administered before dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• New chemical entity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Still in research stage</td>
</tr>
<tr>
<td><strong>Creation of balanced flavour system</strong></td>
<td>Incorporation of a flavour system (sweeteners, buffers, and aromatics) to reduce the aversive taste</td>
<td>• Insufficient for particularly challenging actives</td>
</tr>
<tr>
<td></td>
<td>• Taste-masking via mixture suppression</td>
<td></td>
</tr>
<tr>
<td><strong>Change of API form</strong></td>
<td>Modifying active molecule to one with a lower taste-masking challenge</td>
<td>• Increased development timelines</td>
</tr>
<tr>
<td></td>
<td>• Prodrug</td>
<td>• Potential pharmacokinetic changes</td>
</tr>
<tr>
<td></td>
<td>• Freebase</td>
<td>• May still require other masking technologies</td>
</tr>
<tr>
<td></td>
<td>• Alternative salt</td>
<td></td>
</tr>
<tr>
<td><strong>Complexation of active molecule</strong></td>
<td>API entrapment by chemical matrix</td>
<td>• Decreased drug loading</td>
</tr>
<tr>
<td></td>
<td>• Cyclodextrin</td>
<td>• Potential pharmacokinetic changes</td>
</tr>
<tr>
<td></td>
<td>• Ion exchange resin</td>
<td>• Generally limited to solid forms</td>
</tr>
<tr>
<td></td>
<td>Application of a physical barrier consisting of lipid or polymeric coating</td>
<td>• Potential pharmacokinetic changes</td>
</tr>
<tr>
<td></td>
<td>• Wurster/fluidized bed</td>
<td>• Textural changes (grittiness)</td>
</tr>
<tr>
<td></td>
<td>• Coacervation</td>
<td>• May not be effective on its own depending on API bitterness</td>
</tr>
</tbody>
</table>

Source: David Tisi, Senopsys
a formulator may opt to create a small tablet with a rocking design. In terms of palatability, children prefer flavoured medications, but the opposite is true for older patients. In this case taste-masking polymers can be used to suppress bitterness and achieve a tasteless drug product that also limits drug abuse by children who ‘want more candy’.

**Masking approaches**

In addition to the traditional methods of sweeteners, flavours, buffers, and viscosity and pH modifying agents that help avoid dissolution in the mouth, there are other taste-masking technologies that formulators can utilize. “Other technologies, such as salt formation, prodrugs, complexation, and so on, exist,” explains Karry. “Additionally, coating is gaining further traction in the industry as an effective technology for aggressively bitter APIs.” Limitations of coating techniques include imperfections and adequate in-vivo drug release, she adds.

“Broadly speaking, there are five general masking approaches that are available to the formulator,” states Tisi. “But, each of these approaches comes with its own set of advantages and disadvantages.” (See Table 1)

In terms of future approaches, Tisi believes that there is a trend towards increased multiparticulate dosage forms. “These serve as an alternative to more established formulation options, but generally require extemporaneous preparation in a dosing vehicle—a complexity for some caregiver situations.”

Karry agrees that technologies such as microencapsulation, the addition of pH-modifying agents, suspensions, complex formations, solid dispersions, use of taste suppressants and potentiators, and dry coating bitter APIs are being studied; however, she emphasizes that growth of these technologies is relatively marginal compared with film coating technologies.

**Interesting developments**

“There is continuing interest in the development of a ‘universal’ taste-masking technology that produces small, spherical particles with a polymeric coating optimized for both taste and bioavailability,” notes Tisi. “Advances have been made in these dimensions as well as taste masking; however, bioavailability and manufacturability of a uniform particle size reportedly remains a challenge.”

Basic research into how patients perceive taste is continually advancing with many receptors for sweet and bitter tastes being identified, he adds. “This is enabling screening and identification of compounds that can modulate these tastes,” Tisi explains. “However, for drug products, the regulatory landscape is uncertain for these new compounds.”

 Particularly exciting advances for Tisi are those in the field of signal interruption. “A number of players are now working in this field, and each has a proprietary method for discovering novel taste receptor modulators,” he says. “High throughput screening of candidate compounds is a must, as humans possess more than two dozen known bitter taste receptor cells, and a signal interruption chemical must act on the same set of receptors that the drug does.”

“Now more than ever patients are looking for convenience (i.e., small tablets that can be taken ‘on-the-go’ with minimal or no liquid),” concludes Karry. “As a result, patient convenience and compliance have become important pillars in formulation optimization for new drug products.”

**References**

Research examined the effects of varying excipient and polymer weight in coatings designed to optimize release of diclofenac sodium, with the goal of releasing it at night to improve the treatment of rheumatoid arthritis.

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Accepted: 9 July 2019

Factors affecting drug release
Numerous variables are known to affect drug release from time-controlled compression-coated tablet formulations. They include the viscosity grade of polymer, the amount of polymer, the drug-polymer ratio, and the nature of the drug used in the tablet system \((10,11)\). The research summarized in this article set out to investigate the influence of the type and amount of polymer and the viscosity grade of the polymer in the coat on the time-controlled swelling or rupturing of compression coated tablets.

Materials and methods. DS and hydroxypropylmethylcellulose (HPMC K4M and K15M) were donated by Welable Pharmaceutical Pvt. Ltd., Mehsana. Lactose anhydrous, microcrystalline cellulose (Avicel PH-102), cross-carmellose sodium (Ac-Di-Sol) and magnesium stearate all were purchased from SD Fine Chem Ltd., Mumbai.

Formulation of core tablets. Direct compression was used to prepare the inner-core tablets of DS. Preliminary trials were run to optimize the core tablet (Table I). A powder mixture of the drug, microcrystalline cellulose (Avicel PH-102), lactose anhydrous, cross-carmellose sodium (Ac-Di-Sol), and sunset yellow colouring was dry blended for 30 min in a double-cone blender, after which magnesium stearate and aerosil were added to the blend. It is very important to control the mixing rate with magnesium stearate. The blend was further blended for 5 min and compressed into tablets (with an average tablet weight of 200 mg) using a rotary tablet machine equipped with 7-mm diameter flat punches.

Sufficient pressure was applied to maintain tablet hardness at \(6 \pm 1\) kg/cm\(^2\). After ejection, the tablets were stored over silica gel in a desiccator for 24 hrs to allow for elastic recovery and hardening. Prepared tablets were then evaluated for physical properties such as weight and content uniformity, hardness, friability, disintegration time, diameter, and thickness \((12,13)\).

Selection of polymers for compression coating. Studies used two grades of directly compressible polymer hydroxypropylmethylcellulose (HPLC) K4M (3000–5000 mPas for 2% aqueous solution at 20 °C) and HPMC K15M (12,000–21,000 mPas for 2% aqueous solution at 20 °C) for the time-controlled compression-coated formulation of DS. Both grades are known to form gel under aqueous conditions \((14–17)\).

Preparation of compression coated tablet. A rotary tablet machine was used for compression coating, and the device was maintained at constant pressure, using a two-step direct compression procedure.

In the first step, using the weights listed in Table I, the die was filled with half of the weight amount of polymer to make a powder bed, and the core tablet was placed manually in the center of that bed. In the second step, the remaining half of polymer was added to the die above the core tablet. The powder was then compressed under a sufficient compression force, using a 10-mm diameter flat punch to maintain the coated tablet’s hardness at \(10 \pm 0.50\) kg/cm\(^2\). A standard manual process was used for die filling, core centralization, and machine operation.

Data were then analyzed using a 32 full factorial design. In this approach, two factors were evaluated, each at three levels, and experimental trials were performed at all nine possible combinations (Batches F1 to F9). The experimental design with the corresponding formulations is outlined in Table II.

The independent variables were weight ratio of HPMC K15M to HPMC K4M (\(X_2\)) and amount of polymer (\(X_1\)). Cumulative percentage drug release after 6 hrs (% Q\(_6\)), 750- hrs and 175- hrs (i.e., the time required to release 50% and

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**Table I: Optimized formula for core tablet of diclofenac sodium.**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity (%w/w) per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac sodium</td>
<td>50</td>
</tr>
<tr>
<td>Avicel PH 102</td>
<td>35</td>
</tr>
<tr>
<td>Lactose anhydrous</td>
<td>9.5</td>
</tr>
<tr>
<td>Cross carmellose sodium</td>
<td>4</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1</td>
</tr>
<tr>
<td>Aerosil</td>
<td>0.5</td>
</tr>
<tr>
<td>Sunset yellow</td>
<td>q.s.</td>
</tr>
</tbody>
</table>
75% of the drug respectively) and lag time (in hrs) were selected as dependent variables.

A statistical model (Equation 1) incorporating interactive and polynomial terms was then used to evaluate the responses as:

\[ Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2 \]  

[Eq. 1]

Where \( Y \) is the dependent variable, \( b_0 \) is the arithmetic mean response of the nine runs, and \( b_i \) is the estimated coefficient for the factor, \( X_i \). The main effects (\( X_1 \) and \( X_2 \)) represent the average result of changing one factor at a time from its low to its high value. The interaction terms (\( X_1 X_2 \)) show how the response changes when two factors are simultaneously changed. The polynomial terms (\( X_1^2 \) and \( X_2^2 \)) are included to investigate non-linearity (18).

**Statistical analysis.** Design Expert (Stat-Ease, Inc. Version 9) software using multiple regression analysis was used to analyze results from testing all factorial design batches. The same software was then used to demonstrate, graphically, the influence of each factor on responses, and to generate response surface plots. Coefficients with a p value less than 0.05 (\( p<0.05 \)) were used to look for any significant effects on the prediction efficiency of the model for the measured response.

**In-vitro drug release of compression coated tablets.** In-vitro dissolution studies were then performed on the core tablets and compression coated tablets to verify how the composition of the core and the coat interferes with the drug-release profile. The United States Pharmacopeia–National Formulation (USP–NF) 24 method (basket method, 100 rpm, 37±0.5 °C) was used for dissolution of each of the formulated compression-coated tablets. For the initial two-hour study in 900 mL of simulated gastric fluid, followed by dissolution in simulated intestinal fluid at a pH of 6.8, aliquots of predetermined quantity were collected manually at specific time intervals. Using a UV-visible spectrophotometer at a \( \lambda \) max of 276 nm, they were then analyzed for drug content. All dissolution and lag time studies were repeated three times (\( n = 3 \)).

**Lag time of compression coated tablets.** Compression-coated tablets were placed into a USP dissolution paddle apparatus at a rotation speed of 50 rpm with phosphate buffer

### Table II: Composition for compression coated formulation. HPMC is hydroxypropylmethylcellulose.

<table>
<thead>
<tr>
<th>Batch code</th>
<th>Weight of core tablet (mg)*</th>
<th>Weight ratio of HPMC K15M to HPMC K4M (%)</th>
<th>Weight of polymer used (mg)</th>
<th>Weight of tablet (after compression coating) mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>200</td>
<td>100:0</td>
<td>150:0</td>
<td>350</td>
</tr>
<tr>
<td>P2</td>
<td>200</td>
<td>100:0</td>
<td>200:0</td>
<td>400</td>
</tr>
<tr>
<td>P3</td>
<td>200</td>
<td>100:0</td>
<td>250:0</td>
<td>450</td>
</tr>
<tr>
<td>F1</td>
<td>200</td>
<td>25:75</td>
<td>37.5:112.5</td>
<td>350</td>
</tr>
<tr>
<td>F2</td>
<td>200</td>
<td>25:75</td>
<td>50:150</td>
<td>400</td>
</tr>
<tr>
<td>F3</td>
<td>200</td>
<td>25:75</td>
<td>62.5:187.5</td>
<td>450</td>
</tr>
<tr>
<td>F4</td>
<td>200</td>
<td>50:50</td>
<td>75:75</td>
<td>350</td>
</tr>
<tr>
<td>F5</td>
<td>200</td>
<td>50:50</td>
<td>100:100</td>
<td>400</td>
</tr>
<tr>
<td>F6</td>
<td>200</td>
<td>50:50</td>
<td>125:125</td>
<td>450</td>
</tr>
<tr>
<td>F7</td>
<td>200</td>
<td>75:25</td>
<td>112.5:37.5</td>
<td>350</td>
</tr>
<tr>
<td>F8</td>
<td>200</td>
<td>75:25</td>
<td>150:50</td>
<td>400</td>
</tr>
<tr>
<td>F9</td>
<td>200</td>
<td>75:25</td>
<td>187.5:62.5</td>
<td>450</td>
</tr>
<tr>
<td>P4</td>
<td>200</td>
<td>0:100</td>
<td>0:150</td>
<td>350</td>
</tr>
<tr>
<td>P5</td>
<td>200</td>
<td>0:100</td>
<td>0:200</td>
<td>400</td>
</tr>
<tr>
<td>F7</td>
<td>200</td>
<td>0:100</td>
<td>0:250</td>
<td>450</td>
</tr>
</tbody>
</table>

Note: *Tablet equivalent to 100 mg of drug used. P stands for preliminary batches, F stands for factorial batches.
The lag time was defined as the time point when the outer coating ruptured due to swelling/erosion.

Results and discussion
Pharmacotechnical characteristics of core and compression coated tablets. Core tablets of DS were prepared by direct compression using Avicel PH 102 as a directly compressible excipient, lactose anhydrous as a diluent, and Ac-Di-Sol as a disintegrating agent. The core tablets met all pharmacopoeial requirements in terms of hardness, friability, disintegration time, content uniformity, and weight variation. In 15 minutes of testing, 93% of the drug was released. Upon contact with the dissolution medium, a core tablet began to swell and eventually burst to release the drug. It could be due to porous nature of Ac-Di-Sol. Test results are shown in Table III.

The compression coated tablets were evaluated for the various pharmacotechnical parameters like weight variation, content uniformity, hardness, friability, thickness etc., and all were found to be satisfactory.

Results of preliminary batches. The results of in-vitro release profiles of DS from the preliminary batches (prepared with HPMC K15M and HPMC K4M alone in the outer compression coat in varying amounts) showed that the viscosity grade had a marked effect on drug release rate and lag time. Drug release from the formulations with HPMC K4M (P4-P6) could not be controlled up to 24 hrs because it did not swell homogeneously, and that lack of homogeneity of the HPMC K4M was responsible for the more rapid gel layer formation and higher drug release rate. Formulations with HPMC K15M (P1-P3) can extensively retard the drug release and form a gel more viscous than that formed with K4M and decrease the rate of drug release. Therefore, the study’s aim was to adjust the drug release rate by combining low- and higher-viscosity grades of HPMC.

Drug release mechanism from time-controlled compression coated tablet. Drug is released from compression-coated tablets prepared using HPMC in the outer coat. Both rupture and erosion mechanisms might be responsible for the time-controlled release mechanism. The drug release profile for all formulated batches is given in Figure 2. Drug release kinetics followed zero order and Higuchi suggested controlled drug release from prepared compression-coated tablets. Results of tests involving experimental batches are given in Table IV.

### Table III: Evaluation results of core tablet.

<table>
<thead>
<tr>
<th>Evaluation parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight variation (mg) (n=20)</td>
<td>201± 2</td>
</tr>
<tr>
<td>Drug content (%) (n=10)</td>
<td>97 ± 2</td>
</tr>
<tr>
<td>Diameter (mm) (n=6)</td>
<td>7 ±0.02</td>
</tr>
<tr>
<td>Thickness (mm) (n=6)</td>
<td>4.2 ± 0.05</td>
</tr>
<tr>
<td>Hardness (kg/cm²) (n=6)</td>
<td>6.1 ± 0.4</td>
</tr>
<tr>
<td>Friability (%) (n=30)</td>
<td>0.52±0.2</td>
</tr>
<tr>
<td>Disintegration time (min) (n=6)</td>
<td>12±1.0</td>
</tr>
<tr>
<td>% drug released at 30 min</td>
<td>93 ± 4.0</td>
</tr>
</tbody>
</table>

*All the values are expressed as mean (n=3) ± standard deviation (SD).}

Pharmacopoeia (IP) pH 6.8, 37±0.5°C and observed visually. The lag time was defined as the time point when the outer coating ruptured due to swelling/erosion.

### Figure 2: In-vitro dissolution profile of Batches F1-F9.
Results of polynomial equations and surface response plots

Cumulative percentage drug release after six hrs (% Q_6). The cumulative percentage drug release after 6 hrs is essential because, when the dosage is administered at night (say, at 10:00 PM), symptoms that are experienced in the early morning hrs (i.e., at approximately 4:00 a.m) would be avoided and the drug’s therapeutic effect would be prolonged by continuously releasing the drug over an extended period of time after an administration of single dose. Therefore, % Q_6 was considered as one of the dependent variables in this research. The value of % Q_6 varied from 2.45 to 24.16 for formulated batches and showed a good correlation coefficient (R^2 = 0.9148).

Results from use of the polynomial equation (Equation 2) and surface plot (Figure 3) indicated that both the variables X_1 and X_2 showed significant effect on % Q_6 (p<0.05). As the weight ratio of HPMC K15M to HPMC K4M increased, the % Q_6 value decreased:

\[
Q_6 (%) = +9.96 - 6.21 X_1 (0.0055) - 3.63 X_2 (0.0330) + 0.28 X_1 X_2 (0.8505) + 2.10 X_1^2 (0.3132) + 1.90 X_2^2 (0.3558)
\]

[Eq.2]

Time required to release 50% and 75% drug. The t50- hrs and t75- hrs are important measurements that permit the assessment of drug-release profiles, suggesting the amount of drug available at the site. The t50 and t75 varied from 8.3 to 13.1 and 11.6 to 18.2 and showed good correlation coefficient (0.9827 & 0.9682, respectively). Results of polynomial equations (Equations 3 and 4) and surface plots (Figures 4 and 5), indicated that both the variables X_1 and X_2 showed sig-
significant effect on $t_{50}$ and $t_{75}$ ($p<0.05$). As the weight ratio of HPMC K15M to HPMC K4M increased, the $t_{50}$ and $t_{75}$ values increased:

$$t_{50} \text{ (hrs)} = +10.72 + 1.05X_1(0.0005) + 1.15X_2(0.0004) - 0.025X_1X_2(0.8536) - 0.14X_1^2(0.4388) + 0.16X_2^2(0.3983)$$  \[Eq. 3\]

$$t_{75} \text{ (hrs)} = +15.03 + 1.37X_1(0.0021) + 1.60X_2(0.0011) - 0.050X_1X_2(0.8424) - 0.36X_1^2(0.3116) + 0.34X_2^2(0.3289)$$  \[Eq. 4\]

**Lag time (in hrs).** The time at which drug release began in the dissolution medium was taken as an indication for the lag time. The lag time was found to vary from 2–5 hrs and to show a good correlation coefficient (0.9130).

As the weight ratio of HPMC K15M to HPMC K4M increased, so did the lag time (Figure 6). This may be due to the structural reorganization of hydrophilic HPMC polymer.

An increase in the amount and viscosity of HPMC may result in an increase in the gel strength of the polymer and increased mechanical strength of the coating, reducing medium-permeation rate and resulting in longer lag time. Results of analysis using a polynomial equation (Equation 5) and surface plot (Figure 7), indicated that both the variables $X_1$ and $X_2$ showed significant effect on lag time ($p<0.05$).

As the weight ratio of HPMC K15M to HPMC K4M increased, the lag time also increased.

$$\text{Lag time (hrs)} = +3.71 + 0.75X_1(0.0105) + 0.67X_2(0.0157) + 0.25X_1X_2(0.2841) - 0.18X_1^2(0.5371) - 0.43X_2^2(0.1810)$$  \[Eq. 5\]

**Figure 8** shows overlapping contour plots of all the dependent variables. The highlighted area in the graph suggests the optimized batch area, which exactly matched the input variables value and output value of Batch F5 (for which the weight ratio of HPMC K15M to HPMC K4M (%) was 50:50 and the amount of total polymer was 200 mg).

**Validation of the statistical model.** To validate the statistical model, a checkpoint batch was prepared by taking the level of $X_1=-0.45$ and $X_2=0.45$. The values of $X_1$ and $X_2$ were then substituted in the equations to obtain theoretical (predicted) values.

Comparison of experimental versus predicted values showed that the predicted error varied between -7.14 and +2.77 for prepared formulation. Thus, predicted and experimental values showed reasonably good agreement. Experimental results are given in Table V.

**Conclusion**

A time-controlled, pulsatile release tablet of DS was successfully developed to enable nocturnal dosing for the treatment of rheumatoid arthritis. When taken at bed time, the dosage form has been designed to release active ingredient in the
early hours of morning when patients typically report experiencing more pain.

Controlling lag time and drug release
In formulating this tablet, lag time was controlled by varying the amount of polymer in the outer compression layer. Drug release, meanwhile, was controlled by varying the nature and viscosity of the grade of HPMC polymer that was used.

By combining grades of HPMC of different viscosities, and using them in varying amounts, research showed that it is possible to obtain a lag time of 4–6 hrs, and to control release of the drug for up to 24 hrs. Meeting these performance specifications would be necessary for any pulsatile controlled drug delivery system.

References

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Transdermal drug delivery offers benefits such as needle-free delivery and easier self-administration. Microarray patches are one type of transdermal delivery in which a set of microscopic projections (i.e., microneedles) that contain a liquid drug are applied to the skin using a bandage-like patch. PATH is a nonprofit, global health organization that has been investigating transdermal drug delivery patches for more than 10 years. In August 2018, the organization launched the Microarray Patch (MAP) Center of Excellence as a four-year initiative to accelerate development, particularly for global health needs, such as vaccines and essential medicines. *Pharmaceutical Technology Europe* spoke with Darin Zehrung and Courtney Jarrahian, directors of the MAP Center of Excellence, about the initiative and some of the challenges they have identified for transdermal patch manufacturing. Zehrung is global programme leader and Jarrahian is a programme advisor, both in Medical Devices and Health Technologies at PATH.

**MAP Center of Excellence**

**PTE:** What is the Microarray Patch Center of Excellence initiative?

**Zehrung and Jarrahian (PATH):** Microarray patches, or MAPs, are an innovative delivery technology in early-stage development that could be used to administer vaccines and drugs without a needle or a syringe. For the past decade, PATH, in collaboration with developers and global stakeholders, has advanced the design and development of microarray patch technology for a range of public health needs, including measles, HIV, influenza, malaria, neonatal sepsis, and polio (1). We recognized challenges—including siloed information and limited opportunities for platform-wide approaches—that we could address to improve efficiency of product development. As a result, PATH formed the MAP Center of Excellence, with support from UK Department for International Development, to catalyze development of this promising technology.

Through the Center of Excellence, our aim is to mobilize stakeholders and coordinate a strategic effort to identify and accelerate MAP technology for high-priority health needs in low- and middle-income countries. Currently, we are one year into this four-year initiative. PATH is working with the MAP developer community and global health stakeholder organizations on six functional areas—programme needs, product development, manufacturing, regulatory, business strategy, and engagement—that are critical to advance this promising innovation.

**Manufacturing challenges**

**PTE:** What are some of the key challenges for manufacturing microneedle patches?

**Zehrung and Jarrahian (PATH):** Establishing scalable, automated, good manufacturing practice–compliant manufacturing processes for MAPs is a major focus area of this technology class and will be critical for its success. Technologies can be adapted from other fields to address challenges of precise loading of very small quantities of liquid into the MAP projections. Minimizing drying time is necessary to enable high throughput. Developing processes with high production yield and efficiency in use of the drug substance is also important for cost and sustainability, particularly for costly APIs.

For delivering drugs that require larger dosages (more than a couple of milligrams), a major challenge is providing sufficient drug loading and release, which can require alternative array designs and larger patch sizes. Under our MAPs for PrEP (pre-exposure prophylaxis) programme, funded by the United States Agency for International Development and the President’s Emergency Plan for AIDS Relief (PEPFAR), PATH has been working with partners to address this challenge to enable delivery of long-acting antiretrovirals and hormonal contraceptives by MAP.

**Vaccines**

**PTE:** What are some of the challenges for developing/manufacturing microneedle patches for vaccines in particular?
**Zehrung and Jarrahian (PATH):**
One key challenge is that vaccines cannot be terminally sterilized. Experts have debated about whether a low-bioburden manufacturing approach will be sufficient from a product quality and risk perspective, or whether vaccine MAPs will have to be produced aseptically, which adds complexity and cost to manufacturing facilities and equipment. In addition, vaccine antigens can lose potency quickly, so formulation optimization to maintain stability is critical, especially if enhanced thermostability is desired.

**PTE:** Have you completed any projects for vaccines patches that have been transferred to commercial use?

**Zehrung and Jarrahian (PATH):** Commercialization is the moonshot. Currently, vaccine MAP development is at preclinical and early clinical stages, and no vaccine products have been commercialized yet. However, to build an evidence base to support future commercialization, we've completed studies evaluating factors that will influence cost-effectiveness (2) and stakeholder acceptability (3) of seasonal influenza MAPs, for example. Several developers have published Phase I clinical study results for influenza vaccine MAPs (4–6). To advance the development of MAPs for measles-rubella (MR) and inactivated poliovirus vaccine, PATH worked alongside other organizations such as the World Health Organization (WHO) and the Bill & Melinda Gates Foundation to develop target product profiles and cost analysis. In Ghana, PATH conducted a user study of MAP prototypes with healthcare workers, mothers, and children (7). PATH participates in the WHO MR MAP Product Development Working Group. Under the Center of Excellence, we are assessing the feasibility and value proposition of MAPs for other vaccines, including hepatitis B, human papillomavirus, rabies, and vaccines delivered during disease outbreaks.

**PTE:** One of the potential benefits of patch delivery for vaccines is storage stability. Can you share some of your findings from your work in this area?

**Zehrung and Jarrahian (PATH):** If MAPs are sufficiently thermostable to not require storage in the traditional cold chain (in which vaccines must be stored between 2 and 8 °C) for part of their storage life, that could facilitate new delivery strategies that have the potential to increase access to vaccination. This access is especially important in countries where the cold chain infrastructure is weak. WHO’s minimum standard for a vaccine to be eligible for licensure for use in a controlled temperature chain (CTC) is stability for a minimum of three days at a temperature greater than or equal to 40 °C (8). MAPs could simplify storage and transport, and ultimately improve vaccine access. CTC storage won’t be feasible for all vaccine MAPs due to inherent stability limitations of some antigens.

PATH has developed the Vaccine Technology Impact Assessment (VTIA) model, which compares the total cost of delivery of different vaccine presentations, including the costs of transportation and storage in the cold chain. Our analyses have found that MAPs eligible for CTC storage can reduce vaccine transportation and storage costs. However, the total impact on the cold chain will depend on the storage volume of the MAP compared to the currently used vaccine presentation and the length of time the vaccine can be stored in a CTC. Many vaccines used in low- and middle-income countries are packaged in 10-dose vials, so MAPs are likely to require more storage space on a per-dose basis, particularly those with an integrated applicator device. But compared to the single-dose vials and prefilled syringes commonly used in high-income countries, MAPs could have a packaged volume advantage.

PATH is also supporting the Vaccine Innovation Prioritization Strategy (VIPS) launched by Gavi, WHO, the Bill & Melinda Gates Foundation, PATH, and UNICEF in 2017. This global initiative aims to drive vaccine product innovation to better meet country needs and to improve immunization coverage and equity. MAPs are among the vaccine product innovations being assessed. Insufficient cold chain capacity has also been identified as a key immunization challenge through VIPS that could be addressed through the use of innovations.

**PTE:** What are the next steps for the Center of Excellence initiative?

**Zehrung and Jarrahian (PATH):** We’re initially focusing on the regulatory and manufacturing pathways for MAP technology as a platform. In partnership with Cardiff University, Wales [UK] we’ve launched an initiative working with industry, regulators, and academia to harmonize MAP definitions, critical quality attributes, and key test methods and will aim to produce a white paper documenting these considerations. We’re assessing manufacturing readiness across the technology class, and we plan to host a workshop in early 2020 to delve into key manufacturing challenges and potential solutions. Related to advancing MAPs specifically for global health impact, we’ll be conducting user needs assessments in low-resource countries and using the information to inform target product profiles for prioritized MAP products. User feedback will help ensure that the product meets the needs of health care workers, patients, and health systems to optimize uptake and impact of MAPs in the future.

**References**

8. WHO, “Immunization, Vaccines and Biologicals, Controlled temperature chain (CTC),” www.who.int. PTE
QbD Takes Shape for Topical Pharmaceuticals

As they seek to increase the number of generics available, regulators are requiring that in-vitro and other test data be used for ANDAs, and promoting the concept of biowaivers that would allow such data to replace costly clinical studies.

Agnes Shanley

Although therapeutic creams and ointments have been in use for centuries, development of topical pharmaceuticals is complex and costly. Many topical formulations involve multiple excipients and active ingredients. Their manufacturing is also expensive, requiring large-scale mixing and heating and precise volume filling and packaging, as Markham Luke, director of therapeutic performance of generic drugs at the US Food and Drug Administration (FDA), pointed out in 2017 (1).

Individual differences between patients increase the challenges involved. On the most basic level, each topical formulation will penetrate the skin differently in individuals of different ages, sexes, and races, and occur at different rates in different parts of the same person’s body, says Vijendra Nalamothu, CEO and chairman of Tergus Pharma, a contract research and development company that specializes in topical pharmaceuticals. “Skin absorption for a psoriasis treatment used on the hands will be very different from that for an alopecia therapy targeting the hair follicles on the scalp,” he says.

Given the variability, cost, and complexity of developing topicals, generic pharmaceuticals have not made significant inroads into the specialized and highly segmented market. At a time when generics account for more than 90% of the drugs prescribed in the United States, 80% of name-brand topical drugs on the market have fewer than three generic equivalents, according to Sam Raney, lead for topical and transdermal drug products at FDA’s Office of Generic Drugs. Most name-brand topicals do not even have one generic equivalent, Raney noted during an FDA workshop held on 30 July, 2019 at the University of Maryland’s School of Pharmacy (2).

Also inhibiting topical generics development is bioequivalence testing, which demonstrates that both name brand and generic release active ingredient where it is needed within the body at the same concentration at the same time and under the same conditions. Bioequivalence for topicals has traditionally been determined in the clinic, using comparative endpoint studies, which can involve “enormous risk and investment,” and require thousands of patients, Raney said. Manufacturers and regulators are establishing a framework for more efficient science-based approaches, not only to testing for bioequivalence but for ensuring product quality. For regulators, the goal is to enable more generic manufacturers to enter the market.

TCS classification

To consider questions of bioequivalence in a more scientific way, regulators developed the Topical Classification System (TCS), a framework analogous to the Biological Classification System (BCS) for solid dosage forms, which classifies them based on solubility, permeability, and dissolution. Just as the BCS allows developers a biowaiver in some cases so they can bypass clinical bioequivalence testing, so does the TCS, Raney explained in a webcast for the Product Quality Research Institute (3).

The Q1 category represents an “outer bound,” for demonstrating qualitative similarity, in which reference and test product both contain the same components, The Q2 category goes a step farther: not only would they have the same components but they’d follow the same exact recipe and composition. Similarity in the Q3 category would mean that, in addition to having the same recipe and containing the same ingredients, the two would show a similar microstructure or arrangement of matter (i.e., physical and structural properties), he explained. This structure would make it “thermodynamically impossible” for them to behave differently, Raney said. Q1 and Q2 similarity might mitigate product failure due to irritation or sensitization, where similar Q3 would reduce the risk of product failure due to differences in pH, polymorphism, rheology, entrapped air, drying rate, and other factors, Raney said, noting that excipients can have a major impact on structural properties (i.e., Q3). Under TCS, Class I topicals (for which Q1, Q2, and Q3 are the same
for both the generic and the reference drug) and Class III topicals (for which Q1 and Q2 are different but Q3 is the same) would be eligible for biowaivers.

Within this framework, in-vitro testing methods (i.e., in-vitro release testing [IVRT], as standardized by the US Pharmacopeia [USP] <1724> using static Franz diffusion cells or in-line devices), physical tests for rheology and viscosity, and in-vitro permeation tests (IVPT), which examine pharmacokinetics of the product, are playing a much more important role in topical product development. As Raney emphasized, no single test can definitively show Q3 microstructural similarity. The tests provide insights into product performance and critical quality attributes such as release rate.

Through the US Generic Drug User Fee Amendments Act (GDUFA), FDA has sponsored research to study in-vitro testing methods, which resulted in product-specific guidance documents for performing bioequivalence testing for topical generics. The agency has published seven product-specific guidance documents specifying how to establish bioequivalence. By September 2019, topicals accounted for 12 of the 45 product-specific guidance documents for complex generics issued by the Office of Generics. Revisions were planned for another S3, representing more than 60% of the total (5).

### References
2. S. Raney, “A Generic Perspective on the Use of In-Vitro Assessment Methods,” a presentation at the FDA meeting: Topical Drugs: Development and Evolution of Science and Regulatory Policy, University of Maryland School of Pharmacy, 30 July 2019.

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### Starting Development With the End in Mind

Vijendra Nalamothu, CEO and chairman of Tergus Pharma, shares his views on how topical development is evolving with Pharmaceutical Technology Europe.  

**PTE:** When did you first start using quality-by-design (QbD) principles for topical development?

**Nalamothu:** As part of the SUPAC (short for Scale-Up and Post Approval Changes: CMC, IVRT and In-Vivo Bioequivalence) initiative (1), we were already using in-vitro release testing methods. So we started to use them to develop a design space for QbD. Back in 2012, we used in-vitro permeation testing (IVPT) plus tests for rheology and viscosity as a way to measure critical quality attributes (CQAs). We then took a deeper dive into determining CQAs using microstructure characterization of topicals, applying specific rheological profiles, such as stress and shear curves, and other methods. The industry took the lead and started to use more of these tools to take a QbD approach to topical development. Now, FDA is requiring that generic pharmaceutical companies use IVPT, rheology, and polymorphic data.

**PTE:** Do you expect FDA to issue more generalized guidance on in-vitro testing for topicals in the future?

**Nalamothu:** FDA has issued seven product-specific guidances so far for topical bioequivalence. There are still some technique and data-related issues to address before a generalized guidance can be published. The most detailed of the product-specific guidances so far was for acyclovir cream, to which many other guidances refer.

**PTE:** Why isn’t development of a more generalized guidance industry guidance for topicals possible now?

**Nalamothu:** One major challenge is the fact that the phenomenon of skin absorption is yet to be thoroughly understood. Systemic absorption is well understood, and we have mathematical models that can be used to predict absorption, but actual skin absorption varies greatly. There is no universal absorption. Instead, it depends on many factors such as the individual, the race, age, and sex of the patient, the type of skin and part of the body involved. Other issues concern the IVPT procedure itself. Performing it correctly requires skilled technicians, and results can vary, due to differences in operator training, instrumentation, and other factors. In addition, unpredictable things can happen during testing. For instance, a single air bubble can form under a skin sample, affecting the data. Finally, there are questions about how to process data, and in particular, how to deal with outliers.

**Reference**

1. FDA, Nonsterile Semisolid Dosage forms: Scaleup and Post Approval Changes: MCM, IVRT and In-Vivo Bioequivalence (SUPAC-SS), May 1997.**PTE**
Residual Moisture Determination in Lyophilized Drug Products

The author provides an overview of common residual moisture methods for lyophilized drug products and key points to consider during method selection and method development.

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Lyophilization is a common step in drug product manufacturing to improve stability of the formulation. Optimization of the lyophilization cycle for each formulation/fill combination includes assessment of the residual moisture level of the lyophilized cake. Residual moisture is a critical parameter for stability of the API in lyophilized drug products, particularly with large-molecule formulations such as monoclonal antibody (mAb) and other protein formulations. Often a minimum moisture level is required for protein structural integrity; however, a maximum moisture limit is implemented to reduce API degradation and ensure elegant cake appearance over time. It is imperative that a suitable moisture method is developed for each product to ensure accurate monitoring of the moisture level. Several methods are commonly used in the pharmaceutical industry for residual moisture determination of lyophilized drug products. Methods range from simple drying of samples (loss on drying [LOD]) to titrations (Karl Fischer [KF]) to complex spectroscopic techniques (near infrared spectroscopy [NIR]). Factors such as sample interference, method accuracy, method range, and ability for non-destructive measurement must be considered when choosing an appropriate method for each product. The intent of this article is to provide an overview of common residual moisture methods for lyophilized drug products and discuss the key points to consider during method selection and method development.

Importance of residual moisture
Drug product formulations for many types of molecules are not stable in aqueous solution and often require refrigerated or frozen conditions or the addition of excipients to prevent degradation. Protein and mAb formulations are particularly susceptible to aggregation, deamidation, oxidation, and other degradation pathways not only in solution, but as freeze-dried solids. Residual moisture acts as a plasticizer in predominantly amorphous systems and lowers the glass transition temperature, Tg, of the formulation (1). Even relatively small changes in residual moisture can lead to significant changes in both physical stability and solid-state chemical stability. These types of degradation are more likely to occur with higher levels of water in the formulations; therefore, lyophilization is an appropriate processing step to remove moisture from the formulation. In the lyophilization process, the solution is frozen, then a high percentage of water is removed through sublimation of the ice under low pressure during the primary drying process. This is followed by the secondary drying process, during which the product temperature can be increased to remove additional water to meet moisture level specifications. Optimization of the lyophilization cycle is required to achieve acceptable cake appearance and reconstitution time without comprising the drug activity and stability. Some residual moisture remains in the drug product after lyophilization and must be measured and monitored as part of lyophilization secondary drying process development, product characterization, and stability studies. While low residual moisture levels may seem ideal to prevent degradation, an intermediate level of residual moisture may be needed to ensure acceptable protein activity and reconstitution of the sample (1). Too low residual moisture may cause aggregation, loss of protein activity, reconstitution issues, or even impact further processing steps such as viral inactivation for safety purposes (1, 2). The ability to determine the residual moisture of drug products with acceptable accuracy and precision is crucial for product characterization and stability to ensure the moisture levels remain within the desired range of values. Water may be present in lyophilized samples as bound (absorbed), surface (adsorbed), or trapped (1, 3, 4). Use of different methodologies for residual moisture analysis may yield variable results depending on which type of water is being measured. Typically, residual moisture for lyophilized drug products reflects the amount of surface water present (1, 4).

Compendial moisture methods
Standard-setting organizations such as the US Pharmacopeial Convention (USP) include chapters for well-established moisture methods that are routinely used for residual moisture determination in lyophilized drug products (Table I). While these methods are well-established techniques, they still
must be assessed for specificity, accuracy, linearity, precision, and range for products labelled as meeting good manufacturing practice (GMP) requirements.

Loss on drying (LOD) is the simplest and oldest technique for residual moisture analysis and may be performed without any specialized laboratory equipment. The sample is removed from the vial and weighed into a dried container. The sample is dried using heat, vacuum, or desiccant to remove moisture, then it is cooled and reweighed. The amount of moisture present is calculated by dividing the weight lost during drying by the original weight (5). While this method is simple, it lacks the accuracy and specificity required for most applications. The loss on drying test yields the amount of weight lost only and is not specific for water. Larger sample amounts are needed than with other methods, which can require multiple vials for low-fill products. Other volatiles in the product such as ethanol may also be driven off, yielding inaccurate results. Sample degradation may occur with higher temperatures, which may contribute to falsely high results particularly with proteins. Incomplete drying of samples may yield falsely low results. The technique is very sensitive to test conditions, such as how sample containers are dried and stored, how quickly and uniformly the sample is prepared, how the sample is cooled after drying, and how quickly

<table>
<thead>
<tr>
<th>Method</th>
<th>Sample size</th>
<th>Moisture specific?</th>
<th>Destructive?</th>
<th>Approx. testing time per sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;731&gt; Loss on drying</td>
<td>1–2 g</td>
<td>No</td>
<td>Yes</td>
<td>4 hours</td>
</tr>
<tr>
<td>&lt;891&gt; Thermal analysis</td>
<td>≥ 2 mg</td>
<td>No¹</td>
<td>Yes</td>
<td>1 hour</td>
</tr>
<tr>
<td>&lt;921&gt; Water determination (KF)</td>
<td>≥ 10 mg</td>
<td>Yes</td>
<td>Yes</td>
<td>15 minutes</td>
</tr>
<tr>
<td>&lt;1119&gt; Near-infrared spectroscopy</td>
<td>1 vial</td>
<td>Yes²</td>
<td>No</td>
<td>1 minute</td>
</tr>
</tbody>
</table>

¹Only specific for moisture if coupled with mass spectrometry or other equivalent technique.
²Calibration curve correlating near-infrared spectrum with moisture must be created
measurements are obtained after drying to prevent ambient humidity contamination. Test conditions can be especially critical for hygroscopic samples or high humidity laboratories. These factors all contribute to poor accuracy and reproducibility when compared to other methods.

Thermogravimetric analysis (TGA) is a similar technique to LOD, but with the advantage of being able to use a smaller sample size and having improved control over weighing and temperature. The sample is removed from the vial and weighed into an analysis pan inside a low humidity glove box. The analysis pan is sealed for transfer to a commercially available instrument, which is comprised of a programmable oven and microbalance (6). The weight of the sample is continuously monitored while the temperature is increased from ambient to a temperature that will drive off water without degrading the sample. Similar to LOD, method development is required to determine the appropriate temperature and time required for the sample to reach a constant weight and moisture cannot be distinguished from other volatiles that may evolve at lower temperatures. TGA may be combined with other techniques such as mass spectrometry to differentiate which transitions are due to residual moisture and which are related to other volatiles (1). Drawbacks of TGA include the need to open the sample vial and lack of specificity for water.

Karl Fischer (KF) titration was first developed in 1935 (7) and is based on the generation of iodine and water as reactions reach the endpoint. For volumetric KF titration, the iodine is generated electrically from iodide in the KF reagent when the drift in weight measured is above a defined threshold. Once the drift drops below a setpoint due to all the water in the system reacting with the free iodine, the instrument stops producing iodine and the titration reaches the endpoint.

In coulometric KF titrators, iodine is generated electrochemically by the instrument through anodic oxidation of iodide in the solution (Equation 2):

\[ 2 \text{I}^- \rightarrow \text{I}_2 + 2\text{e}^- \]  

(Eq. 2)

The iodine reacts with water in the sample. Once all water has reacted with iodine, the generation of iodine stops and the titration ends. The amount of water present is determined by measuring the current and duration of the reaction (Equation 3):

\[ (\text{RNH})\cdot\text{SO}_3\text{R} + 2\text{RN} + \text{I}_2 + \text{H}_2\text{O} \rightarrow (\text{RNH})\cdot\text{SO}_4\text{R} + 2(\text{RNH})\text{I} \]  

(Eq. 3)

Measurement of residual moisture in lyophilized products is usually performed using coulometric KF titration, per United States Pharmacopeia (USP) <921>, Method lc (9). KF analysis may be performed using manual titration but is most commonly performed using commercially available instrumentation. Commercial reagents and standards are also available, which allow for easy implementation in quality control (QC) laboratories, operation by entry-level scientists, and consistency between laboratories. Coulometric titration is preferred over volumetric titration because lower moisture readings are more accurate and reproducible using this technique.

In coulometric KF titrators, iodine is generated electrically from iodide in the KF reagent when the drift in moisture measured is above a defined threshold. Once the drift drops below a setpoint due to all the water in the system reacting with the free iodine, the instrument stops producing iodine and the titration reaches the endpoint. For volumetric KF titration, the iodine is delivered from a buret as needed, and the solution is standardized for calculation of the residual water in the sample (7). Coulometric KF instruments are available with or without a diaphragm to separate the anode and cathode. Instruments without a diaphragm require only one reagent and reduction of iodine back to iodide at the cathode is prevented by the design of the instrument. Instruments with a diaphragm require separate analyte and catholyte reagents for operation and are preferred for very low levels of moisture typically found in lyophilized drug products, as reactions reach the endpoint more quickly, and the instrument is more accurate and precise at lower levels.

Lyophilized samples may be analyzed by direct addition to the titrator or by external extraction using an anhydrous solvent. Typically, extraction using anhydrous methanol is the preferred method because the drug product sample container has minimal exposure to the laboratory environment and methanol is compatible with the KF reaction. Direct addition of the sample to the titrator requires opening the product vial, transferring material to weigh on a balance, and then opening the KF titrator to add the sample. These steps all allow for environmental moisture contamination of the measurement. External extraction requires analysis of a blank measurement to subtract the diluent moisture content from sample results, but substantially reduces exposure of the sample to the environment. Anhydrous methanol is transferred to a stopped container to reduce gradual increase of moisture in the diluent during the test duration. Lyophilized samples are generally stoppered with partial vacuum in the headspace, which can impact the accuracy of the weighed vial; therefore, any vacuum in the sample container is released using a dry syringe needle prior to weighing. Syringes and needles are used to reconstitute the lyophilized sample with anhydrous methanol, and the sample is mixed by vortex mixing or sonication to dissolve or suspend the cake solids. Both the weight of the lyophilized cake and the diluent added must be determined. The reconstituted solution is analyzed by KF, and then the moisture content of the cake is calculated by subtracting the diluent moisture level. Duplicate or triplicate analysis of samples is recommended to ensure reproducible results. Common issues during KF analysis include sample interference and sample dissolution difficulties. Many drug product formulations include excipients or active ingredients that interfere with the KF reaction, such as reducing agents like ascorbic acid which react with the iodine in solution or boron compounds like boric acid which react with the methanol to yield water (7, 10). Both types of interference yield artificially high moisture results. Performance of spiking studies to determine accuracy and linearity are essential in verifying that no side reactions are occurring that may artificially inflate results. While complete dissolution of the cake in the extraction solvent is not required for reliable, accurate results, incomplete dissolution can result in lower moisture
values, clogged syringes, and poor precision. The diluent may be modified to include other reagents, such as formamide for sugars, sugar alcohols, and proteins, which may improve dissolution. Interference due to the presence of ketones or aldehydes in the sample may be overcome using special KF reagents that contain different alcohols or increasing the pH (7).

Sample interference may often be overcome using KF instruments with an oven attachment. With an oven, the sample is heated, and moisture is driven into the titrator via dry air or nitrogen so that the sample never directly contacts the KF reagent. Because only the moisture is titrated, side reactions are often eliminated. Use of a KF Oven instrument does require the development of appropriate settings for oven temperature, run time, and endpoint criteria, but enables moisture analysis using a well-established and accepted technique. Use of a KF Oven typically requires opening the sample vial to transfer weighed material to an analysis vial, and so use of a low humidity glove box is recommended, and determination of a method blank is important. Overall, coulometric KF has many benefits and is usually a first-choice method for residual moisture analysis. Tedious manual analysis, use of hazardous reagents, and destruction of the sample are the main drawbacks of this method.

Spectroscopic methods such as near infrared spectroscopy (NIR) have more recently been adapted for residual moisture determination of lyophilized products. The main reason for the popularity of these types of methods is that they enable lyophilized samples to be analyzed non-destructively. Lyophilized samples typically are produced in glass tubing vials which have a flat bottom surface. The spectrum of the cake is read through the bottom of the vial and correlated to the known moisture result using chemometric software. Moisture determination by NIR uses two regions of water absorption: the OH stretch/HOH bend combination band at approximately 5150–5200 cm⁻¹ and the first overtone of OH stretch at approximately 6800–6940 cm⁻¹ (11). The NIR absorption is not a direct measurement of water content. Instead, a calibration curve must be generated using a reference method such as KF, and the KF moisture values are correlated to the NIR spectra. Lyophilized vials spanning the desired region of residual moisture levels are first scanned using the NIR to obtain the spectrum. Then the same vials are analyzed using a reference method such as coulometric KF to obtain the residual moisture. The residual moisture values are then entered into the NIR chemometric software to correlate the values for each vial and create a calibration curve. Several options for correlation are available, including stepwise multiple linear regression (SMLR), partial least square (PLS), and principle component regression (PCR), with PLS being the most commonly used method. The second derivative of the spectrum is used for quantitative analysis. Once the calibration has been created, the correlation must
be evaluated for acceptable fit. The coefficient of determination (R2), root mean square error of calibration (RMSEC), and other software specific values such as Performance Index are useful to assess a good calibration curve (11). Settings for smoothing, minor adjustments for the spectral regions, and removal of outlier values may aid in creating a good calibration. At least 20 independent values are required to provide sufficient data for the correlation. Once a suitable calibration is obtained, a cross-validation is typically performed to further assess performance. One standard is removed from the model at a time, re-calibration is performed, and predicted values are generated. Cross-validation will yield the R2 of cross validation and root mean square error of cross validation (RMSEV), which are useful in comparing calibrations to find the optimal model. Additionally, more lyophilized samples may be scanned by NIR, analyzed by KF, and then predicted results are compared to the KF result. This external cross-validation allows calculation of the root mean square error of prediction (RMSEP) (11).

Drawbacks for this type of method include shifting or shrinkage of the cake within the vials resulting in error in obtaining the spectra, necessity of calibration curve creation for each formulation, needing to validate the chemometric software, and potentially missing moisture in the vial headspace. The laser for NIR systems typically reads about 3–4 mm into the cake, through the glass vial. If the cake does not contact the vial surface, the reading will not be as accurate. Furthermore, lyophilized samples with very low fill volumes may not be suitable if the cake is too thin. Having a cake of “infinite thickness” or more than 4 mm eliminates the need to consider depth of the reading into the sample (12). As described previously, development of NIR methods requires correlation to a direct method, and the reference method must first be validated prior to supporting NIR calibration creation. Within a standard chemometric software there are many mathematical tools to analyze and fit the correlation data, and achieving acceptable correlation may be difficult. Large sample sizes are required, and samples must be available that span the range of anticipated moisture results. Preparing lyophilized samples across a wide residual moisture range may be difficult, because cake meltback may occur at higher moisture levels and spiking samples with water requires care not to dissolve the cake and to ensure moisture is fully equilibrated throughout the cake prior to NIR measurement. Because other components in a formulation, particularly sugars, may yield changes in the NIR spectrum, a new calibration model must be developed for each formulation (11). Chemometric software packages are now available that meet 21 Code of Federal Regulations (CFR) Part 11 requirements, but completing such a validation takes time and resources. Despite these drawbacks and the need for more upfront work, NIR is a useful technique, especially when large numbers of samples must be analyzed, or sample quantities are limited and non-destructive testing is desired.

**Figure 1.** Example near-infrared (NIR) spectra and second derivative spectra for sucrose/glycine samples. Second derivative is used for correlation modeling in the TQ Analyst software (Thermo).

**Figure 2.** Comparison of near-infrared (NIR) predicted and Karl Fischer (KF) moisture values. Vials 17–29 were randomly pulled throughout the lyophilization cycle and were not tested by KF. Vials 45–50 were also not tested by KF, since other similar samples were tested.

**Emerging techniques**

New techniques for moisture measurement continue to be developed. One such instrument is the Vapor Pro Moisture Analyzer manufactured by Ametek (Rx and XL models), which has been evaluated in the lab as an alternative to KF or LOD, especially for samples that are not compatible with the KF reaction or include other volatiles. The lyophilized cake is broken up using a sharp probe by piercing the stopper and is then placed into the heated chamber of the instrument. As the vial is introduced...
Analytics

are required, most side reactions found in KF titration are eliminated, measurement are specific for moisture, lyophilized sample vials do not need to be opened prior to analysis, and the system may be used by operators with minimal training. Drawbacks of this technique are the need for method development to optimize temperature and analysis time, destruction of the sample, and potentially longer run times than KF. Currently, this technique is not listed in regulatory guidelines or compendia. Validation of a method using the Vapor Pro would be conducted in a manner similar to KF.

Other techniques such as frequency modulated spectroscopy (Lighthouse analyzers) are also under development, in which moisture is measured by laser absorption in the gas headspace of a vial through the glass container. The laser is tuned to match the internal absorption frequency of water molecules so that the amount of laser light absorbed is correlated to the amount of water in the headspace. While this technique has advantages of being non-destructive, rapid, specific for water, and easy for operators to perform, sensitivity of the technique for practical use in residual moisture determination has yet to be demonstrated.

Case study: simple lyophilized product

A 25 mg/mL sucrose/25 mg/mL glycine solution was prepared and lyophilized in 20-mL vials. Historical data supported using coulometric KF as a reference method because no interference or solubility issues were anticipated, and a NIR method was desired because several hundred vials would require residual moisture analysis to support residual moisture mapping of production scale freeze dryers. Vials were removed from the lyophilizer at periodic intervals during the secondary drying process using a sample “thief”, to yield samples with varying moisture levels. The vials were allowed to stand for several days so that residual moisture could equilibrate throughout the cake. The NIR spectrum of each sample was recorded in duplicate through the bottom of the vial using the integrating sphere sample model for the NIR (Thermo Antaris II MDS with RESULT software suite for collection and TQ Analyst for calibration model). A total of 51 vials into the instrument, the stopper is pierced by a hollow needle so that dry nitrogen can flow through the sample as it is heated. Moisture is driven off and measured by a calibrated relative humidity sensor. Sensor readings are combined with nitrogen flow and temperature data to yield the sample moisture result. Advantages of the system are that no hazardous reagents are required.
**Partial least square (PLS) technique**, constant pathlength, second derivative, Norris smoothing, and spectral regions of 5203.00–5511.56 cm\(^{-1}\) and 7112.19–7324.32 cm\(^{-1}\). The KF moisture value and the average predicted moisture value from the calibration were compared to check performance of the correlation model. See Figure 1 for example NIR spectra and second derivative spectra and Figure 2 for comparison of KF and NIR predicted moisture results. All predicted results were within ± 0.2 % H\(_2\)O (absolute difference) of the KF result, except for Vial 3, which was atypically high. The curve created would be most suitable for moisture levels between 1% and 4% based on the data points used to create the curve. Vial 3 was more than 6% moisture and did not fit the curve as well (absolute difference was 0.7% H\(_2\)O).

**Case study: small-molecule lyophilized product**

A new residual moisture method was required for a small-molecule product containing ascorbic acid (vitamin C) and mannitol. Previous efforts had utilized coulometric KF and direct addition of the solid to the titrator with unacceptable results. Ascorbic acid is known to interfere with iodine in KF reaction (\(\text{Eq. 4}\)):

\[
C_6H_8O_6 + I_2 \rightarrow C_6H_6O_6 + 2I^- \tag{Eq. 4}
\]

This interference may yield falsely high results, because the ascorbic acid is measured as water by the titrator and may be contributing to high variability of moisture results using the current method. Therefore, a new method for moisture analysis was developed to minimize exposure of the lyophilized product to ambient humidity and improve the accuracy and precision of sample data.

Various techniques for moisture analysis were evaluated with samples to evaluate compatibility with each method type. Samples were prepared for evaluation to contain varying levels of ascorbic acid while keeping other drug product ingredient levels constant, to confirm any impact of ascorbic acid interference on the results. Samples were equilibrated for a few days with stoppers removed in a desiccator filled with saturated potassium hydroxide (KOH) having a relative humidity of approximately 8.2% to ensure that all vials were equivalent in moisture prior to testing. Vials were stopped after equilibration under conditions of low humidity (approximately 20%) in a nitrogen-purged glove box. Samples were analyzed by NIR, and 32 vials were analyzed in triplicate by KF using extraction by anhydrous methanol. The KF values were correlated with the appropriate spectra using Thermo TQ Analyst software to create a calibration curve. A model was created using partial least square (PLS) technique, constant pathlength, second derivative, Norris smoothing, and spectral regions of 5203.00–5511.56 cm\(^{-1}\) and 7112.19–7324.32 cm\(^{-1}\). The KF moisture value and the average predicted moisture value from the calibration were compared to

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**Table II. Summary of Karl Fischer (KF) oven spiking study results with anhydrous methanol diluent. RSD is relative standard deviation.**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Theoretical spike</th>
<th>Experimental spike</th>
<th>% Recovery</th>
<th>% RSD triplicate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.80</td>
<td>0.57</td>
<td>72</td>
<td>8.2</td>
</tr>
<tr>
<td>2</td>
<td>2.28</td>
<td>1.74</td>
<td>76</td>
<td>2.0</td>
</tr>
<tr>
<td>3</td>
<td>3.25</td>
<td>2.56</td>
<td>79</td>
<td>4.1</td>
</tr>
<tr>
<td>4</td>
<td>4.35</td>
<td>2.97</td>
<td>68</td>
<td>11.4</td>
</tr>
<tr>
<td>5</td>
<td>6.24</td>
<td>4.74</td>
<td>76</td>
<td>1.5</td>
</tr>
<tr>
<td>6</td>
<td>8.27</td>
<td>6.14</td>
<td>74</td>
<td>2.9</td>
</tr>
</tbody>
</table>

**Figure 6. Summary of Karl Fischer (KF) oven spiking study results in anhydrous methanol diluent.**

**Figure 7. Summary of Vapor Pro spiking study results.**

**Table III. Summary of Vapor Pro spiking study results.**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Theoretical spike %</th>
<th>Experimental spike %</th>
<th>% Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.98</td>
<td>0.91</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>2.08</td>
<td>2.17</td>
<td>104</td>
</tr>
<tr>
<td>3</td>
<td>4.31</td>
<td>4.18</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>6.05</td>
<td>6.15</td>
<td>102</td>
</tr>
<tr>
<td>5</td>
<td>8.22</td>
<td>8.23</td>
<td>100</td>
</tr>
</tbody>
</table>
Analytics were analyzed by KF using anhydrous methanol extraction, KF Oven, and Vapor Pro. LOD was not evaluated as a potential method because it is not specific for moisture analysis. NIR was not pursued at this time due to low projected sample testing requirements. Vials containing the target amount of ascorbic acid were spiked with water to evaluate method accuracy. Only KF Oven and Vapor Pro were used to evaluate spiked samples due to the known interference of ascorbic acid with KF results.

For KF titration, each vial was weighed (w1v) and then reconstituted with 5 mL of anhydrous methanol. The diluent weight was recorded (wd), and the vial was vortex mixed for 30 seconds to mix. Each sample was analyzed in triplicate. The vials were rinsed and dried, and the empty vial weight was obtained (w2v). The moisture of each cake was calculated as shown in Equation 5:

\[
\%\text{Water}_{\text{sample}} = \frac{(%\text{H}_2\text{O}_{\text{sample}} \times (w_{1v} + w_{D} - w_{2v})) - (w_{D} \times %\text{H}_2\text{O}_{\text{diluent}})}{(w_{1v} - w_{2v})}
\]

[Eq. 5]

For KF Oven, each sample vial was weighed (w1v) and then reconstituted with 5 mL of anhydrous methanol (wD). Vials were vortex mixed for 30 seconds. Extraction was used with the oven sampler to avoid the interfering ascorbic reaction while also not having to open the product vial containing dried material. Approximately 1 g of this solution was transferred to a KF Oven vial and sealed. Each sample was analyzed in triplicate. Samples were analyzed using an oven temperature of 110 °C, nitrogen flow of 150 mL/min (2.0 psi), mix time of 1800 s, max time of 600 s, and end criteria of ≤ 5 µg/min. The mix time describes the time when the sample vial is lifted into the oven so that moisture begins to be released, but the nitrogen flow is bypassed so the titration does not start yet. The titration begins, nitrogen flows through the sample vial in the oven, and the titration starts. The titration ends when the maximum time or drift rate is reached. Sample vials were rinsed, dried, and weighed (w1v). The moisture of each cake was calculated as above, using a vial filled with anhydrous methanol for a blank.

For Vapor Pro, each sample vial was weighed (w1v, g). The lyophilized cake

### Table IV. Summary of repeat Karl Fischer (KF) oven spiking study with anhydrous methanol:formamide (2:1) external extraction. RSD is relative standard deviation.

<table>
<thead>
<tr>
<th>Spike level</th>
<th>% SpikeExperimental</th>
<th>% SpikeTheoretical</th>
<th>% Spike recovery</th>
<th>% RSD / % Diff.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.781</td>
<td>0.613</td>
<td>127.3</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>0.581</td>
<td>0.605</td>
<td>96.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.608</td>
<td>0.637</td>
<td>95.4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.321</td>
<td>2.367</td>
<td>98.1</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>2.440</td>
<td>2.190</td>
<td>111.4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6.317</td>
<td>5.930</td>
<td>106.5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>6.552</td>
<td>5.810</td>
<td>112.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.730</td>
<td>3.941</td>
<td>120.0</td>
<td></td>
</tr>
</tbody>
</table>

### Figure 8. Plot of repeat Karl Fischer (KF) oven spiking study using anhydrous methanol:formamide (2:1) extraction solvent.

### Table V: Comparison of methods developed for case study with small-molecule formulation containing mannitol and ascorbic acid.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vapor Pro method</th>
<th>KF oven method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>No vitamin C interference; specific for moisture as shown by linearity, accuracy, precision</td>
<td>No vitamin C interference; specific for moisture as shown by linearity, accuracy, precision</td>
</tr>
<tr>
<td>Linearity</td>
<td>R2 = 1.00 over range</td>
<td>R2 = 0.99 over range</td>
</tr>
<tr>
<td>Accuracy</td>
<td>92–104% spike recovery over range</td>
<td>95–127% spike recovery over range</td>
</tr>
<tr>
<td>Precision</td>
<td>Visually assessed from supporting study (Figure 5) and suitable for use as a moisture method</td>
<td>6–17% over range</td>
</tr>
<tr>
<td>Range</td>
<td>1–8% spiked water</td>
<td>1–6% spiked water</td>
</tr>
</tbody>
</table>
was broken up using a sample breaker (needle-like tool inserted through the stopper). Each vial was analyzed using a temperature setting of 110 °C and a nitrogen flow of 75 ± 2 mL/min. Stop criteria for the analysis included a minimum time of 10 minutes, followed by a rate criteria of ≤ 0.05 µg/s. After analysis, the vial was rinsed, dried, and weighed (w2v, g). The percent moisture of each cake was calculated by dividing the amount of water measured by the weight of the sample cake [(µg water/ (w1v – w2v)] x (1 g/106 µg) x 100]. The entire vial is then analyzed immediately for Vapor Pro.

Samples analyzed by KF using anhydrous methanol extraction were difficult to dissolve in methanol and showed a proportional increase in apparent residual moisture with respect to increase in ascorbic acid (Figure 3) demonstrating that KF is not suitable for the product. Samples analyzed by KF oven with anhydrous methanol extraction were quite variable and even negative, likely due to very low moisture levels in the product which may have been below the sensitivity of the instrument (Figure 4). No trend in moisture relative to ascorbic acid content was observed. A diaphragm-less cathode must be used for KF oven instruments, which impacts instrument sensitivity. Samples analyzed by Vapor Pro showed improved precision and no trend in moisture related to ascorbic acid content (Figure 5).

The spiking study for the KF oven using anhydrous methanol showed that results were linear (R2 = 1.00), but not as accurate as expected (Figure 6). All recoveries were near 75%, supporting that some aspect of the spiking technique or measurement technique was impacting the result. Spiking of the methanol diluent instead of direct addition of water to the sample has been performed with success for other KF accuracy studies and may yield improved accuracy results here as well. Precision for triplicate measurements was acceptable at 2–11% (Table I).

The spiking study for Vapor Pro showed that Linearity was acceptable (R2 = 1.00), and accuracy was also acceptable with recoveries of 92–104% (Figure 7 and Table III). Precision could not be evaluated because only one vial was analyzed at each level, but previous Vapor Pro studies demonstrated acceptable precision.

Though the Vapor Pro method demonstrated better precision, accuracy, and linearity than the KF Oven method, additional method optimization and evaluation were performed for the KF Oven method in an effort to yield a suitable method that complied with USP <921>. An extraction solvent consisting of anhydrous methanol/formamide (2:1) with KF oven analysis was found to yield more consistent results for samples, indicating that the samples may not have dissolved well in previous KF oven testing, leading to falsely low residual moisture values. The anhydrous methanol/formamide (2:1) mixture was used to repeat a spiking study for the KF oven. Sample vials were equilibrated to constant humidity, and approximate moisture levels were evaluated by NIR before spiking to ensure that spectra for each vial matched.

The repeat spiking study for KF oven with anhydrous methanol/formamide (2:1) diluent was assessed for recovery/accuracy, precision, and linearity. Moisture for an unspiked sample was used to determine the spike recoveries for each level. Spike recoveries ranged from 95–127%. Precision ranged from 6–17%. Linearity was evaluated by plotting the experimental spike recovery vs. the theoretical spike recovery. Linearity was demonstrated, with an R2 value of 0.99 (Table IV, Figure 8).

For this case study, suitable Vapor Pro and KF oven methods were developed for residual moisture analysis of the drug product containing mannitol and ascorbic acid (Table V). Method validation would be required prior to using either method for testing for GMP purposes. Ultimately, the KF oven method was chosen using the anhydrous methanol/formamide (2:1) diluent because this technique is described in USP <921>, Method 1c (9).

**Conclusion**

Residual moisture is a critical attribute of lyophilized drug product formulations, and suitable methods must be developed to accurately measure residual moisture for drug product characterization and stability. Methods should be specific for water, and coulometric KF, NIR, and emerging techniques such as Vapor Pro are favored over non-specific methods such as LOD and TGA. Method development must include evaluation of interfering reactions and sample solubility for KF methods and potential for heat degradation for oven methods. Sample analysis from an unopened lyophilized vial is preferable, and creation of a NIR calibration curve should be considered for larger projects where the additional work would be a worthwhile investment in the long term. All methods should be validated prior to use for GMP testing, including spike recovery studies.

**References**

6. USP <891>, “Thermal Analysis” (US Pharmacopeial Convention, Rockville, MD, 2019).
Evaluating the Technology Transfer Process

Unforeseen challenges can be avoided in tech transfer by evaluating the variety of processes involved.

Susan Haigney

Technology transfer is a multifaceted task that involves different departments and expertise within a pharmaceutical organization. It is a task, therefore, that can come with unforeseen challenges, even when the process may seem simple, according to Joerg Zimmermann, vice-president Vetter Development Service at Vetter Pharma-Fertigung GmbH & Co. KG. Pharmaceutical Technology Europe spoke with Zimmermann about the tech transfer process and how companies can make this transfer as painless as possible.

Beginning the tech transfer process

PTE: What are the first steps that should be taken when starting the process of transferring information and processes from one group or company to another?

Zimmermann (Vetter): I think the most important thing is to perform a combination of a gap and risk analysis between the existing process at the sending site and the envisioned process at the receiving site. This practice assists in identifying and evaluating the manufacturing and testing steps along with organizational issues and logistics, and it assesses the risk of identified differences between the transfer sites. In the spirit of International Council for Harmonization (ICH) Q8(R2) Pharmaceutical Development (1): the results of a thorough evaluation of the quality target product profile (QTPP) of the product and the associated critical quality attributes (CQAs) define the scope of the transfer.

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

Zimmermann (Vetter): Certainly, as open communication and trust is key. The closer the sending and receiving sites work together, the better the transfer will work out. The sending site will usually have years of practical experience and defined routines, while the transfer itself offers the opportunity to redesign and modernize elements of the process. Wherever possible, you should involve the people that are actually making and testing the product since a good deal of know-how is not actually in the documents themselves, but in the heads of the people involved!

PTE: How does tech transfer differ between in-company transfers and sponsor/contract facility transfers? Are the process steps different?

Zimmermann (Vetter): In general, there is no difference either in the process itself or in the regulatory aspects. However, there may be underlying resistance from the sending site in the case of a sponsor. This is something that must be dealt with within the ‘cultural’ part of the project. Procedurally, there will always be differences in the ways of working, including the quality systems. As such, these too must be evaluated.

Evaluating processes during tech transfer

PTE: Which manufacturing processes should be evaluated when it comes to tech transfer?

Zimmermann (Vetter): All processes should be evaluated from start to finish including all unit operations. For aseptic fill/finish operations, processes would include compounding, sterile filtration, filling, visual inspection, and secondary packaging.

PTE: Which analytical processes should be evaluated in tech transfer?

Zimmermann (Vetter): There will always be several analytical processes that need to be transferred, for example, in-process testing as well as release testing. The extent of the transfer itself depends on the analytical capabilities of the receiving site. It is possible to establish and run all analytical procedures, be they chemical, biological, microbiological, or physical tests for in-process testing, product release testing, and stability testing. The test can be something simple like pH, or more complex like an SDS–PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis) for proteins.
PTE: Which quality and/or validation process should be evaluated in tech transfer?

Zimmermann (Vetter): The inception of any process transfer is the process qualification campaign, which is based on [the US Food and Drug Administration’s] FDA’s approach of first (process design), second (process qualification), and third (continuous process verification). Its purpose is always to achieve a robust, reproducible manufacturing process with consistent quality at the receiving site.

Operations in tech transfer

PTE: Which team members/departments should be included in the tech transfer process?

Zimmermann (Vetter): Process transfers are usually run as projects with dedicated cross-departmental teams. These include development, manufacturing operations, quality assurance and quality control, qualification/validation, and regulatory affairs. It also includes production planning and logistics. All are organized and coordinated by a project manager who reports to the project sponsor. Ideally, all functions from both sites are involved to a certain extent with respective partners in the other organization. In this way, subject matter experts can directly communicate with their peers.

PTE: How can tech transfer operations affect current/other manufacturing operations both at the sponsor site and the outsourcing site?

Zimmermann (Vetter): It is the nature of the business that to a certain extent, the introduction of new products and processes will interrupt running operations. Thus, the goal is to always keep interruptions to a minimum. The receiving site should always have a vested interest in both a smooth transfer and a robust process as they will be running it for years, or even decades into the future.

PTE: Are there specific tools used in tech transfer? If yes, what, where, and why?

Zimmermann (Vetter): Most certainly. Strong project management is paramount in any tech transfer. The roles and responsibilities for all team members must be agreed upon and a system that enables adequate communication and feedback of information must be established. All pharmaceutical process steps can be directly derived following ICH Q8(R2) (1) and FDA guidance (2). Based on prior knowledge of similar products and processes, a smooth and swift process transfer can be designed and executed.

References
1. ICH, Q8 (R2) Pharmaceutical Development (ICH, August 2009).
The Cost of Brexit

Despite preparative work by the bio/pharma industry, any Brexit scenario will result in regulatory implications and increased costs.

Vincenzo Salvatore
is team leader Healthcare and Life Sciences Focus Team, BonelliErede.

At the time of writing this article, it is still unknown as to whether or not the United Kingdom, pursuant to Article 50 of the Treaty on European Union, will reach an agreement establishing the arrangements for its withdrawal from the EU. If Brexit leads to the UK leaving the EU without a withdrawal agreement in place, there will be a so-called ‘hard Brexit’, which will make citizens, companies, and public authorities, on both sides of the English Channel face a critical time as the UK, from 1 November 2019 onwards, will cease to be bound by the rules on free movement of goods, workers, and services. Alternatively, should a further extension to reach an agreement be granted, as most people currently predict will be the outcome, pending the negotiations on the new set of rules for governance, a transitional period, with no major changes to the current relationship, will commence, and likely run until 31 December 2020, leading to a so-called ‘soft Brexit’. In either scenario, the bio/pharma industry has been preparing to mitigate the impact of Brexit by undertaking a Brexit impact assessment and addressing the major implications that the UK’s withdrawal from the EU will have on their internal organization and marketing strategies. Regulatory authorities (inter alia, the European Medicines Agency (EMA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA)) and governmental institutions (mainly the European Commission (EC) and the UK’s government) have issued and constantly updated several publications that identify the major challenges and provide all the relevant stakeholders with valuable guidance on how to best prepare for change in their respective fields, especially in the case of a no-deal Brexit.

Major issues for consideration

Among the major issues the bio/pharma industry will have to consider is the relocation of European headquarters or, at least, a relevant portion of staff, as EU legislation applicable to both the pharmaceutical and medical device industries requires companies to be established in the EU (rectius, in the European Economic Area [EEA], including Norway, Iceland, and Liechtenstein) to keep on benefiting from the EU internal market. According to Article 2 of Regulation (EC) No. 726/2004, the marketing authorization holder must be established in the EU (1). Through the EEA agreement, this is extended to include also Norway, Iceland, and Liechtenstein (2). Conversely, with specific regard to the marketing of medicinal products in the UK, the marketing authorization holder and the qualified person for pharmacovigilance (QPPV) should be established in the UK by 31 July 2021 at the latest (3).

Additional implications to be duly taken into account relate to the need for compliance with new customs formalities (e.g., import and export licences issued in the UK will be no longer be valid in the EU) and tax procedures (e.g., EU member states will charge VAT [Value Added Tax] at importation of goods entering the EU from the UK). Import and export burdens in trading with the UK are likely to generate delay or, in the worst-case scenario, a shortage of products on the UK market. According to the Serious Shortage Protocols (SSPs) (4), which may be issued when it is deemed to be absolutely necessary, pursuant to the Human Medicines (Amendment etc.) (EU exit) Regulations 2019, which amends the Human Medicines Regulations 2012, UK pharmacists may be given unprecedented powers to substitute drugs they are unable to get hold of, for other drugs, which may not necessarily have the same active ingredients as those prescribed (4). As far as medical devices are concerned, in the case of a ‘no-deal’ Brexit, UK-based notified bodies will no longer be recognized by the
Import and export burdens in trading with the UK are likely to generate delay or in the worst-case scenario a shortage of products on the UK market.

EU after Brexit, meaning that the devices they have certified will no longer be in conformity with the applicable EU rules and, as such, they will not be able to be placed on the EU market. That’s the reason why the British Standards Institution (BSI) group, the UK national standard body, chose Amsterdam for its second location and migrated most of its clients and certificates to the Netherlands to reduce the risk of a ‘no-deal’ Brexit.

In addition, bio/pharma companies have to bear in mind that the UK will be progressively losing its clinical trial attractiveness as many research and development activities have already moved outside the UK to remain eligible and approvable for the EU market. This will also be the consequence of unsecure access to the Horizon Europe, the next EU research and innovation framework programme 2021–2027 that will replace Horizon 2020, and on uncertainty related to the future mobility of researchers, scientists, and other employees of the pharmaceutical and medical device sectors (5). Access to the EU research and development funding could only be retained through the UK gaining the ‘associate member’ status for Horizon Europe, that still has to be negotiated.

Increased costs: Financially and socially
All the above-mentioned changes imply an increase in activity-related costs for the bio/pharma industry, irrespective of the final Brexit outcome scenario. Nonetheless, the magnitude of market disruptions and financial implications will greatly depend on the actual exit scenario.

According to the Queen’s speech addressed to both Houses of Parliament on 14 October 2019 (6), the UK government intends to work towards a new partnership with the EU, based on free trade and friendly cooperation. This approach seems to entail an option where UK remains part of the European Economic Area (EEA), retains access to the EU market, and is allowed to take part in clinical trials EEA (or Norwegian model). Should the latter not be the case and omitting all the possible intermediate variations of the aforesaid option, the worst-case scenario would imply a complete separation of the UK market from the EU where World Trade Organization rules apply. That would probably lead to the negotiation of mutual recognition agreements to give effect to authorizations and certificates issued by the UK, EU, and EU member states’ competent authorities, respectively. The same may be true with regard to technical standards that medical devices will have to comply with to be placed on the market.

Looking at individuals it has been highlighted that patients, researchers and scientists, medical practitioners, and public health groups are also expected to greatly suffer from the UK divorce from the EU. Industry will have to take this element in due consideration as this will constitute an obstacle to health-related mobility that may seriously undermine not only the patients interests but also training and condition of work of healthcare professionals. This will definitely have a serious impact on future research activities and on the supply-demand ratio for both medicinal products and medical devices.

Avoiding major disruptions
Eventually, it has to be noted that at this point in time the UK government is committed to ensure that EU rules are converted (‘grandfathered’) into UK law at the moment of exit through the EU (Withdrawal) Act, with changes where necessary to make sure the rules work in the UK.

The magnitude of market disruptions and financial implications will greatly depend on the actual exit scenario.

In addition, whatever the final exit scenario will be, adequate time will be given for businesses to smoothly implement any new requirements. Furthermore, information that is already available will also be used to complete administrative tasks for continuity of work and authorizations.

Last but not least, the bio/pharma industry is expected to cooperate with governmental authorities in promoting information and awareness campaigns to avoid consumer panic and major disruption on the availability of medicinal products and medical devices on both the UK and the EU internal market.

References
3. MHRA, “Further Guidance Note on the Regulation of Medicines, Medical Devices and Clinical Trials if There’s No Brexit Deal,” gov.uk, 3 September 2019.
**PRODUCT/SERVICE PROFILES**

**Continuous Flow Development for Efficient Chemical Synthesis**

**Description**
Cambrex has invested strategically at key development and manufacturing facilities to expand its capabilities to include continuous flow technology, for fast and efficient chemical synthesis in API manufacturing.

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To complement its capabilities in Karlskoga, Cambrex has installed and validated multiple continuous flow reactor platforms at its US centre of excellence for API clinical supply and process development in High Point, North Carolina. This facility focuses on the rapid development of processes to supply clinical as well as commercial demand for chemical syntheses.

More information on Cambrex’s continuous flow capabilities and experience can be found at www.cambrex.com/resources

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**Zydis® Ultra, a Next-Generation ODT Dosage Form**

**Description**
Catalent’s Zydis® oral disintegrating tablet (ODT) technology is a unique, freeze-dried tablet that disperses almost instantly in the mouth without water. Zydis is recognized as one of the world’s best performing ODTs and has well-established advantages over conventional oral dosage forms, including improved patient compliance, adherence and convenience. To date, more than 36 products have been launched using Zydis technology in over 60 countries.

Earlier this year, Catalent announced it is to invest more than $27 million at its Swindon, UK facility to commercialize Zydis® Ultra, its next-generation ODT technology.

Zydis Ultra is a patented, taste-masking technology that uses acoustic mixing to form a micronized polymeric coating over an API. This coating allows increased drug loads to be introduced during a product’s formulation, enabling the dosage of active ingredient to be up to four times higher than a conventional Zydis ODT without impacting oral disintegration time or drug performance.

Catalent
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**Description**
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Our system is regularly inspected by the competent local authorities and many pharmaceutical customers (e.g., Novo Nordisk, Sanofi, Boehringer Ingelheim, Eli Lilly, Novartis, MSD, Roche, Pfizer).

Our major services along the supply chain are loading with dedicated equipment, dedicated tank trucks, dedicated tank farms, clean-room repackaging, analytical testing, and lot-specific COAs released by a QP (Ph. Eur). All our products fulfil the highest quality expectations (GMP) and knowing the requirements of our customers, we offer the full regulatory service including the possibility of audit reports and quality agreements.

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**Nexera Prep Series**

Shimadzu’s new Nexera Prep Series Preparative Purification Liquid Chromatograph (LC) provides better prep processes for extraction of functional and impurity components, as well as purification of target compounds in the pharmaceutical, chemical, and food industries. This product dramatically improves productivity via flexible scalability and an efficient, user-friendly preparative workflow.

The Nexera Prep Series consists of multiple related products with the LC units as the core. Users select a pump, autosampler, and detector to build a system according to the purpose of the preparative work. Systems can be configured using related products such as the LH-40 Liquid Handler, FRC-40 Fraction Collector, Shim-pack Scepter LC Column for Analysis and Preparative Work, and Column Hub.

**Lonza Engine™—Accelerate Innovation**

Lonza Engine™ offers state-of-the-art equipment designed to address the needs of customers throughout the entire drug development process including:

- Liquid filled hard capsules filling and sealing equipment: support for lipid-based formulations to improve the bioavailability of poorly soluble compounds
- Micronization equipment: flexible solution for micronization process, including different technologies and containment solutions for particles engineering
- Powder micro-dosing system: precise filling of capsules without excipients or bulking agents.

As an extraordinary value-add to our customers, Lonza’s expert team of technical service engineers work with manufacturers all over the world to help improve their operational efficiency. We are committed to providing full manufacturing support—including onsite problem resolution—for Capsugel® products and equipment.

**Process2Clean: CIP Detergents**

VAI’s Process2Clean cleaning products are specifically formulated for critical process cleaning applications. Each detergent is engineered to effectively remove numerous product residues found in pharmaceutical, biotechnology, medical device, and research & development industries. Process2Clean detergents successfully remove existent residues present in process manufacturing and reduce them down to acceptable trace residual limits. This critical process assures that product contact surfaces are clean prior to subsequent manufacturing and reduces the possibility of product contamination or product adulteration.

Process2Clean detergents include an Alkaline Detergent, an Acid Based Detergent, a Hydroxyacetic Acid Cleaner, a General Purpose Cleaning Detergent, a Neutral pH Cleaning Additive, and a Chlorinated Alkaline Cleaning Detergent. This complete line of detergents are capable of removing a wide range of residues from inorganic to organic process soils and can be used in numerous cleaning systems from automated to manual.

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**Shimadzu Europa**

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shimadzu@shimadzu.eu

**Veltek Associates, Inc.**

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Gerresheimer Renovates Glass Production Facility

Gerresheimer completed a modernization of its plant in Essen, Germany, including renovation of its clear-glass furnace used to produce glass containers for the pharmaceutical industry, the company announced in an 28 Oct. 2019 press release. The improved furnace technology is more powerful but uses less energy, making it more sustainable than its predecessor. The high-performance furnace also adds new capacity for the production of injection and infusion bottles from type II glass for parenteral solutions.

“We want to make production more environmentally friendly while remaining an efficient partner for our customers,” said Dr. Jürgen Unruh, CEO of Gerresheimer Essen, in the release. According to the release, Gerresheimer is using the renovation as an opportunity to fundamentally modernize the plant. The production hall and cleanroom will be enlarged, and the testing and packaging technology will be further automated. The energy efficiency of the new white glass tank will be improved while at the same time reducing specific carbon dioxide emissions. In addition, a new candle filter sustainably reduces nitrogen oxide content.

The company’s plant in Essen serves as a center of excellence for the production of type II glass. The Gerresheimer Group has production sites for moulded glass in Europe, the Americas, and Asia.


GE Healthcare Inaugurates Open-Access Lab at Alderley Park

GE Healthcare has announced the inauguration of an open-access lab at the Mereside Campus of Alderley Park in the United Kingdom, which will be used to support acceleration of biotech, health, and life-sciences research.

The new lab will feature advanced protein and cell analysis technologies to support small and medium-sized enterprises (SMEs) from early stage R&D to process development through to manufacturing. Additionally, it is hoped that valuable insights into the challenges faced by SMEs will be gained from the experiences with the open-access lab, allowing for the development of solutions that could benefit the whole life-sciences community in the UK.

“We’re thrilled to be launching this facility which will help accelerate our customers’ research and discovery aims,” said Kath Mackay, manager director, Alderley Park, in the press release.

“The new GE laboratory is an excellent addition to the highly specialized scientific services offered at the Park and complements the existing oncology, analytical, and open access services.”

Conor McKechnie, chief marketing officer, GE Healthcare Life Sciences, added, “The start-up community at Alderley Park has the creativity, vision, and scientific expertise to help transform medicine. Providing them access to our technologies and services is a natural part of our mission to accelerate and advance biopharmaceuticals.”


Sartorius Signs Acquisition Agreement for Danaher Life Science Platform Business

Sartorius has signed an agreement for the acquisition of parts of Danaher’s Life Science Portfolio in cash. The transaction will include the label-free biomolecular characterization (FortéBio), chromatography hardware and resins, and microcarriers (SoloHill) businesses. The agreement is subject to Danaher’s acquisition of the GE Biopharma business, in addition to any related regulatory approvals.

“The portfolio proposed for acquisition represents an excellent strategic fit with Sartorius,” said Joachim Kreuzburg, Sartorius’ CEO, in a press release. “With the Octet platform of FortéBio, we will add a broadly accepted and differentiated technology for advancing and simplifying drug discovery to our lab division’s portfolio…”


GammaDelta Therapeutics Announces Spin-Out Company Formation

GammaDelta Therapeutics has unveiled the formation of a new spin-out company, Adaptate Biotherapeutics, aimed at developing antibody-based therapies that modulate gamma delta T-cells.

In an 16 Oct. 2019 press release, it was revealed that the new spin-out company will build on GammaDelta’s knowledge so that it is possible to regulate gamma delta T-cell activity through the use of therapeutic antibodies with the potential to trigger an immune response against cancer. Particularly, Adaptate Biotherapeutics will develop a number of potential drug targets and antibodies, discovered by GammaDelta, for therapeutic purposes and to advance them into the clinical trial stages. The current chief scientific officer of GammaDelta, Natalie Mount, will move over to the spin-out company, becoming its chief executive officer.


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It is good industry practice to clarify the precise remit for each of the reviewers of a controlled document, says Siegfried Schmitt, PhD, vice-president, technical, Parexel Consulting.

**Q.** In a recent audit, we were asked about the meaning of the signatures on our controlled documents. Our reply was that it clearly states that the signatories are either authors, reviewers, or approvers. The auditor considered our response insufficient, pointing out that we often have up to 10 reviewers. Though the names and titles of these are given, their review responsibilities are not defined or described. We are unclear how to make the meaning of the signatures more precise.

**A.** The regulations do not provide much detail with regards to your question. For example, the European Union guidelines (1) require, “Documents containing instructions should be approved, signed, and dated by appropriate and authorised persons.” The US regulations are a little bit more specific in 21 Code of Federal Regulations (CFR) Part 11 (2) regarding the signing of electronic records and state, “This information must include the printed name of the signer, the date and time when the signature was executed, and the meaning [emphasis added] (such as review, approval, responsibility, and authorship) associated with the signature.”

The question is whether the meaning of the signatures in your documents is clear enough and unambiguous. Let us look at an example, such as a cleaning standard operating procedure (SOP) for manufacturing equipment. An author, most likely a member of the operations team, prepares the document. There will be several reviewers, possibly including manufacturing, engineering, validation, quality unit, regulatory affairs, and health and safety. These reviewers will each have a different perspective from which they perform their review.

One could argue that the role and the associated job description define sufficiently what a reviewer has to do. In theory, yes; but in practice this is often not the case. Therefore, companies typically apply one of two approaches: either define the controlled documents review and approval responsibilities in a document (e.g., the SOP for SOPs) or add the meaning to each signature in the signature list.

Table I is an example of such a review responsibilities matrix. If we apply this to the cleaning SOP example, we would expect:

- The operators to check if the instructions can actually be performed (technical feasibility)
- Managers in manufacturing to check the functional correctness of the cleaning procedures (e.g., cross-reference cleaning validation reports) and to verify that the instructions are clear and logical
- The validation team to verify that the cleaning procedures are in concurrence with previously executed cleaning validations
- The quality unit to ensure that the document uses the correct template and format, that the procedure meets regulatory requirements, and that any related change controls or audit/inspection commitments have been met
- The regulatory affairs department to confirm that the procedure is in concurrence with the manufacturing licenses
- The health and safety executive to check that all required safety precautions are applied, for example, where flammable or corrosive solvents are used.

In summary, it is good industry practice to clarify the precise remit for each of the reviewers of a controlled document, rather than just apply the general term of ‘reviewer.’ This does not have to be as difficult as the example herein. And finally: are you still sure you need up to 10 reviewers?

**References**

1. European Commission, EudraLex Vol. 4 Part I Chapter 4 Documenta-
2. Electronic Records; Electronic Signatures, Federal Register 62 (54), 20

**Table I: Example review responsibilities matrix.**

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<th>Functional manager</th>
<th>Quality unit</th>
<th>Regulatory affairs</th>
<th>Health and safety</th>
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- Quality of information/text review | -Compliance with the regulations review
-Compliance with the quality system review
-Format/layout review | -Compliance with the marketing authorization review |
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One system, two methods. HPLC meets UHPLC

The Nexera-i MT simplifies the transfer of existing HPLC to faster UHPLC methods. It assures high cross-compatibility between the former and new method conditions. Nexera-i MT is based on the compact i-Series platform of HPLC and UHPLC systems and targets a wide range of industries, such as pharmaceuticals, chemicals and foods.

HPLC and UHPLC analysis on a single system using a dual flow path for automated switching between HPLC and UHPLC analyses

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