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In announcing a new report on drug shortages, FDA noted “their [drug shortages] impact is likely underappreciated” (1). The seriousness of shortages of crucial drugs is not lost on doctors, caregivers, and patients.

For example, the ongoing heparin shortage has caused surgeons to reconsider heart surgeries and implement emergency plans. Drugs for childhood cancers, palliative care, septic shock, anesthesia, and sedation are also experiencing shortages. In addition, ongoing shortages are not being resolved. In fact, after declining from a peak in 2011, the number of ongoing drug shortages has increased, with some shortages continuing for eight years.

While production- and quality-related issues have previously been cited as the reasons specific drugs may experience shortages, the report had a direct assessment of the root cause: economic factors are the cause of drug shortages.

Under the direction of Congress, FDA in July 2018 established an Agency Drug Shortages Task Force, which was charged with identifying the root causes of drug shortages and suggesting potential long-term solutions. The task force included representatives from FDA, the Centers for Medicare & Medicaid Services, and other federal agencies impacted by drug shortages.

The resulting report, “Drug Shortages: Root Causes and Potential Solutions” (2), published in October 2019, was based on FDA analysis of data on 163 drugs that went into shortage from 2013 to 2017, as well as comparisons to similar drugs that were not in short supply. The report also considered published research, comments at public meetings, and input from representatives from the public and private sectors. Not surprisingly, drugs that are relatively low in price, “financially un-attractive” drugs, and sterile injectables are more likely to be in short supply.

The task force’s report identified an unusual business pattern that does not follow “textbook” practices during a product shortage. After a typical shortage, the report said, prices go up and other suppliers are incentivized to enter the market. With drug shortages, this scenario does not occur.

Instead, “prices rarely rose after shortages began, and during shortages, production typically did not increase enough to restore supply to pre-shortage levels. Many manufacturers reported discontinuing the production of drugs before a shortage for commercial reasons (e.g., loss of profitability),” FDA reported in a statement announcing the report. “These results suggest a broken marketplace, where scarcity of drugs in shortage or at risk for shortage does not result in the price increases predicted by basic economic principles,” the statement continued.

Three root causes identified are a lack of incentives for manufacturers to produce less profitable drugs; no recognition for manufacturers that have mature quality systems that focus on continuous improvement and early detection of supply chain issues; and logistical and regulatory challenges make it difficult to recover from a disruption.

The task force suggested a shared understanding of the impact of drug shortages be created, including quantifying the harms of shortages, developing a quantitative characterization of the shortage, and more transparent pricing from contract manufacturers. Development of a rating system to encourage drug manufacturers to invest in quality management maturity for their facilities, and the promotion of sustainable private sector contracts to make sure there is a reliable supply of important drugs were also suggested.

References
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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

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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.

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Deitz Company
www.Deitzco.com
EVENT OVERVIEW:
Currently, the pharmaceutical industry rarely takes sustainability into the raw material sourcing decisions, yet, various aspects of the pharmaceutical ingredient sourcing process offer opportunities for the industry to advance sustainability goals. This webcast will provide insight on how sustainably sourcing raw materials for the manufacture of pharma ingredients can contribute to sustainability and potentially give companies a competitive advantage in the marketplace. Experts will explore the importance and benefits of sourcing sustainable palm and palm kernel oil-based products and will discuss BASF’s commitment to offering only oleo chemicals certified from the Roundtable on Sustainable Palm Oil (RSPO)-certified palm and palm kernel oil.

- Sustainable sourcing of excipients: contributing to sustainability and developing a competitive advantage
- RSPO certification defined
- BASF oleo product offering and its impact on customers; overview of BASF RSPO certified oleo product offering

Key Learning Objectives
- Gain insights on the sustainable sourcing landscape
- Learn how pharma ingredients derived from RSPO-certified palm and palm kernel oil can contribute to your sustainability goals
- Impact of BASF’s move to offer only oleo chemicals derived from RSPO certified palm and palm kernel oil

Who Should Attend
- Managers in pharmaceutical procurement responsible for buying pharma ingredients
- Sustainability management in Big Pharma
- Formulators of products where sustainability may be a core differentiator

Presenters
Frank Romanski, PhD
Head of Global Marketing, BASF Pharma Solutions

Sebastian Form
Director of Applied Sustainability
BASF Nutrition & Health

Moderator
Kaylynn Chiarello-Ebner
Managing Editor, Special Projects
Pharmaceutical Technology

For questions contact Kristen Moore at KMoore@mmhgroup.com
More Consistent Drug Inspection System on Horizon

Jill Wechsler

FDA readies more efficient oversight processes while advancing collaboration with Europe.

Continuing concerns about the quality and safety of prescription drugs, particularly APIs and products made overseas, has spurred efforts by FDA to modernize its drug manufacturing inspection programs at home and abroad to better detect potentially harmful and violative medicines, while streamlining oversight for reliable producers. The ongoing discovery of potential carcinogens in multiple formulations of medicines with ranitidine has prompted recalls, Congressional investigations, and a clamor for more effective oversight of drugs and their ingredients.

To address these and other long-term concerns, FDA’s Office of Regulatory Affairs (ORA) is moving forward with efforts to roll out a much-discussed New Inspection Protocol Project (NIPP), a key component of its initiative to make field inspections more efficient, predictable, and informative (1). ORA is applying the new process first to sterile products in recognition that most serious manufacturing problems and related drug shortages involve contaminated or violative sterile injectables. ORA has conducted several pilot programs to test new methods for inspecting and evaluating manufacturing processes and facilities for sterile drugs and continues to fine tune the program with an eye to full implementation in the near future. Other dosage forms, including bulk powders, transdermal delivery systems, creams, solutions, metered-dose inhalers, terminally sterilized products, and APIs will fall under the NIPP in coming years.

The NIPP is part of a major reorganization of the ORA field force over the past decade, which has established dedicated cadres of investigators for drugs, biologics, medical devices, and other regulated products (2). The aim is to shift the focus of inspections to practices and metrics related to achieving and maintaining a state of quality production, explained Rosa Motta, supervisory consumer safety officer in the Center for Drug Evaluation and Research (CDER), at the PDA/FDA Joint Regulatory Conference in September 2019.

These changes have taken several years to implement, but now the NIPP appears to be near the starting gate. The ability of inspectors to collect data in a structured manner and to submit them in templated inspection reports will enable data analysis that can help focus future inspections on key areas and support informed and data-driven decisions on product and process quality, Motta noted. FDA also is beginning to construct surveillance and pre-approval protocols for inspections of non-sterile products, with plans to follow with similar approaches for API inspections.

**Seeking better responses**

A related inspection initiative aims to address manufacturer complaints that investigators raise unexpected and sometimes unfounded issues during site visits, leading to noticeable variation in citations for violative actions. In response, FDA has launched an initiative to improve communications about and industry responses to Form 483 notices issued to companies at the conclusion of site inspections. Agency inspectors use this process to inform a manufacturer of the observations made during the inspection affecting product quality, including the scope of the issues, impact on other drugs, and whether the observations appear to be isolated incidents or global in nature, explained David Jaworski, senior policy advisor in the Office of Manufacturing Quality in CDER’s Office of Compliance, at the PDA/FDA conference.

Manufacturers are expected to address Form 483 observations following an inspection through a comprehensive investigation and development of a corrective actions and preventive actions (CAPA) plan. To avoid delays and often inadequate industry responses, FDA officials seek to provide more details and advice on how companies should meet these obligations. The first step, Jaworski advised, is for the manufacturer to fully understand the Form 483 observations to investigate the issues and conduct a risk assessment on the relative severity of each observation for patient health and product quality. Such analysis then forms the basis of a CAPA plan that describes immediate short-term corrective actions and strategies for addressing root causes of larger or systemic issues. Jaworski also advised manufacturers to submit clear responses—preferably in English—that identify the facility involved and observations addressed.

Jill Wechsler
Pharmaceutical Technology’s Washington editor, jillwechsler7@gmail.com.
The larger objective is to facilitate corrective actions, while also enabling FDA to issue warning letters expeditiously when warranted. Clear communications between field inspectors and company officials aims to improve the process for identifying quality problems and making necessary changes leading to long-term improvements.

**Sharing inspection reports**

In addition to updating FDA inspection practices, the ORA field force aims to reduce the need to visit capable and compliant manufacturing facilities in Europe and other regions through full implementation of the Mutual Recognition Agreement (MRA) for drugs with the European Union (3). Under development for a decade, the MRA capability assessment process was completed by FDA and EU regulatory officials in 2019. It is now being implemented so that regulatory authorities may share inspection and quality information and recognize and rely on GMP inspections in each other’s territory. This process is expected to provide a “significant” drop in inspections in both regions. noted David Churchward, deputy unit manager at the UK’s Medicines & Healthcare Products Regulatory Agency (MHRA), at the PDA/FDA conference, citing a 75% reduction in EU inspections in the United States.

Churchward further pointed out that an important benefit for US manufacturers is an end to the requirement that products shipped to EU member states have to submit to EU quality control testing to be imported. While there is no obligation for regulators to accept an inspection report from another agency, all parties may do so, and also stand to benefit from mutual alerts to problems and shared database information on good manufacturing practice issues. Efforts are underway to build confidence further for relying on reports for pre-approval inspections and for third-country site visits. Also planned are efforts to negotiate a similar agreement for veterinary medicines and to extend the drug MRA program to vaccines by 2022. Differences in oversight of clinical trial operations, though, has put on hold for now plans to harmonize inspections in that area.

**References**

1. FDA, “Statement from FDA Commissioner Scott Gottlieb, M.D., on New Steps to Strengthen and Modernize Agency’s Oversight and Reporting of Inspections for Sterile Injectable Drugs,” FDA.gov, Nov. 9, 2019.
The Right Pieces for a Quality Program

Susan Haignorey

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

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 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.

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 fulfill 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
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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 must 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 some 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,” Ginsbury continues. “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].”

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 (QA) 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.

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.”

**Need for independence**

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, 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 program 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, 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 out of specification 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.

Procedures and personnel
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 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.

**Rapid and thorough response**

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.” says Moreton. “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 press 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. FDA, Responsibilities of Quality Control Unit, 21 CFR §211.22.
6. FDA, Current Good Manufacturing Practice In Manufacturing, Processing, Packaging, Or Holding Of Drugs; General, Definitions, 21 CFR §210.3 (15).
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Adapting APIs for Specialty Dosage Forms

Cynthia A. Challener

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

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 non-uniform 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 pediatric 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 pediatric patient group is unique, adds Anthony Qu, vice-president of scientific affairs for Cambrex. “The pediatric patient population includes infants, children, and adolescents. You cannot simply cut an adult dosage down. Pediatric 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 pediatric 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.
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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, swallowing capability 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 pediatric 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 pediatric 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?

“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, flavors, 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 Qu. 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 often suitable for pediatric 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. On the other hand, these formulations typically contain sorbitol, which could have potential side effects in children. Other factors to consider, 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 pediatric 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 pediatric 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 pediatric 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. “Selecting suitable excipients for a pediatric 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 pediatric and other specialty formulations requires extensive knowledge and expertise in not only a wide 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

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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 irritation (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.”

Karry continues by specifying that in her opinion the second and most important challenge in bitter formulations is to prevent drug release in the mouth. “Human saliva has a pH range between 6.2 and 7.6,” she states. “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...”
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for complete polymer solubilization in the stomach even with shorter gastric residence times (1 hr) or when the patient is in a fed state (pH 4.2–5.8),” she says. “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 flavors) 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.

<table>
<thead>
<tr>
<th>Approach</th>
<th>Mechanism</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signal interruption</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>• Taste masking via mixture suppression</td>
<td>New chemical entity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Still in research stage</td>
</tr>
<tr>
<td>Creation of balanced flavor system</td>
<td>Incorporation of a flavor 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>Change of API form</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>Complexation of active molecule</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>Physical encapsulation</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>

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

Source: David Tisi, Senopsys

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 pediatric 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 a formulator may opt to create a small tablet with a rocking design. In terms of palatability, children prefer flavored 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, flavors, 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 I.)
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**

“The 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**

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 Pharmacopeia 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 labeled 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 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 electrons during the reaction of iodide and water, as follows (8).

Alcohol (typically methanol) and sulfur dioxide mix in a basic solution (typically imidazole) (Equation 1):

\[ \text{ROH} + \text{SO}_2 + \text{RN} \rightarrow (\text{RNH})-\text{SO}_3\text{R} \]  \hspace{1cm} \text{(Eq. 1)}

Iodine is generated electrochemically by the instrument through anodic oxidation of iodide in the solution (Equation 2):

\[ 2\, \text{I}^- \rightarrow \text{I}_2 + 2\, \text{e}^- \]  \hspace{1cm} \text{(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).

\[ (\text{RNH})-\text{SO}_3\text{R} + 2\text{RN} + \text{I}_2 + \text{H}_2\text{O} \rightarrow (\text{RNH})-\text{SO}_4\text{R} + 2(\text{RNH}_2) \]  \hspace{1cm} \text{(Eq. 3)}

---

**Table I. United States Pharmacopeia methods for residual moisture analysis of lyophilized drug products.**

<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.
Measurement of residual moisture in lyophilized products is usually performed using coulometric KF titration, per United States Pharmacopeia (USP) <921>, Method Ic (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 anolyte 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 stoppered container to reduce gradual increase of moisture in the diluent during the test duration. Lyophilized samples are generally stopped 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 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. Tedium 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.
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TruCLEAN Mop Frame
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TruCLEAN Adjustable Handle
Lightweight handle with super-smooth finish to prevent microbial growth.

TruCLEAN Wringer
Unique wringing action significantly improves release of contaminants.

36 Liter Bucket
Temperature-resistant polypropylene with embossed graduations.

TruCLEAN Mop Frame
Easily maneuvered over floors, walls, ceilings, and baseboards.

Capture and isolate contaminants effortlessly. Compact design simplifies use in confined areas. Includes high-grade stainless steel components and temperature-resistant polypropylene buckets.

Compatible with gamma, ethylene oxide, and autoclave sterilization.

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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 up-front 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.

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 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, 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 solu-
bility 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 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 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% H₂O (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% H₂O).

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 (Equation 4):

\[
C₆H₈O₆ + I₂ → C₆H₄O₆ + 2I^⁻ \quad [Eq. 4]
\]
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 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 evaluated spiked samples due to the known interference of ascorbic acid with KF results.

For KF titration, each vial was weighed \( w_1 \) and then reconstituted with 5 mL of anhydrous methanol. The diluent weight was recorded \( w_d \), and the vial was vortex mixed for 30 seconds. Each sample was analyzed in triplicate. The vials were rinsed and dried, and the empty vial weight was obtained \( w_2 \). The moisture of each cake was calculated as shown in Equation 5:

\[
% \text{Water}_{\text{sample}} = \frac{\left( \% H_2O_{\text{sample}} \times (w_1 + w_d - w_2) \right) - \left( w_d \times \% H_2O_{\text{diluent}} \right)}{(w_1 - w_2)}
\]

For KF Oven, each sample vial was weighed \( w_1 \) and then reconstituted with 5 mL of anhydrous methanol \( w_d \). 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.
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VISION
A resilient Joint Force enabled to fight and win unencumbered by a chemical, biological, radiological, or nuclear environment; championed by innovative, agile, results-oriented acquisition professionals.

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- Proteins on Demand
- Animal models for arena, filo, alpha viruses
- Animal models for burkeholderia spp, and coxiella
- Platform based MCM targeting bacterial and viral threats agents
- Host/Immune modulators as short term anti-infectives-(bacterial and viral)

- Distributed Biological Reconnaissance
- Unattended Perimeter Monitoring
- Emerging/Novel Biological Threat Sensing
- Medical Artificial Intelligence

- Autoinjector Development and Drug Manufacture to Deliver MMB4/Atropine
- Single Chamber Autoinjector to Deliver Small Molecule Nerve Agent Therapeutic

Medical CBRN Defense Consortium
Other Transaction Agreement (MCDC OTA)
FY-19-21 Forecast
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 (w2v). The moisture of each cake was calculated by dividing the amount of water measured by the weight of the sample cake, in other words, (µg water/(w1v – w2v)) x (1 g/106 µg) x 100. The entire vial is analyzed at once 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 has been performed with success for other KF accuracy studies and may yield improved accuracy results here as well. Precision for triple measurements was acceptable at 2–11% (Table II).

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
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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) 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

### 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></td>
<td>6.317</td>
<td>5.930</td>
<td>106.5</td>
<td></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>

### 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 (<a href="#">Figure 5</a>) 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>

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

Contin. on page 56
The concept of pulsatile release, in which active ingredient is fully and quickly released after a predetermined lag time, is gaining popularity as a drug-delivery approach. Pulsatile release offers a way to counteract the “first-pass” effect, and to enable nocturnal dosing. This article summarizes research into optimizing the formulation of pulsatile release tablets that contain diclofenac sodium (DS), an anti-inflammatory used to treat rheumatoid arthritis. Studies focused on optimizing the formulation of a time-controlled tablet containing the active ingredient in its inner core, surrounded by a coating of hydrophilic polymers.

As the fields of chronopharmaceutics and chronopharmacology (1) reveal more about the importance of circadian rhythms with respect to human physiology, disease state, and drug action, time-controlled pulsatile-release tablets are being considered as a desirable drug-delivery mode. Research discussed in this article focused on compression coating, which can involve direct compression of both the tablet’s core and its coat, obviating the need for separate coating processes and the use of coating solutions. Compression-coated formulations can be used to protect hygroscopic, light-sensitive, oxygen- or acid-labile drugs, or to separate incompatible drugs from each other. They can also be used to achieve controlled release, and a number of studies (2) have evaluated compression-coated time-controlled drug delivery systems. Most of these formulations release the drug after a lag phase.

Compression is easy to achieve on a laboratory scale. The technique requires relatively large amounts of coating materials, however, and it is difficult to position the cores correctly (3). For pulsatile release, modifications are made to the outer layer of the tablet during formulation development to control the lag time prior to release of the drug from the tablet’s inner core (4–5). Studies used Penwest’s TIMERx technology (6) (Figure 1) to formulate the tablets, which are comprised of an inner core that contains the drug and an outer layer that has been compression-coated with a hydrophilic matrix of the heteropolysaccharides xanthan and locust bean gum (7).
The goal of this work was to formulate compression-coated tablets, taking human circadian rhythms into account, using pulsatile delivery of DS to modulate the drug level for optimal treatment of rheumatoid arthritis (8,9).

In this study, a time-dependent compression coated system of DS was developed to target drug release in the colon. If the formulation could be developed so that the required dose of DS could be administered at night, at around 10 PM, it was believed that patients’ morning pain symptoms could be avoided. The drug’s therapeutic effect could also be prolonged by continuously releasing the medication over an extended period of time after the administration of a single dose.

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, micro crystalline 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 coloring was dry blended for 30 min in a double-cone blender, after which magnesium stearate and aerosol were added. 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 ± 1 kg/cm². 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 ± 0.50 kg/cm². A standard manual process was used for die filling, core centralization, and machine operation.

### 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>
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 (X1) and amount of polymer (X2). Cumulative percentage drug release after 6 hrs (% Q6), t50- hrs and t75- hours (i.e., time required to release 50% and 75% of the drug respectively) and lag time (hrs) were selected as dependent variables.

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

\[ Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \]  
[Eq.1]

Where Y is the dependent variable, \( b_0 \) is the arithmetic mean response of the nine runs, and \( b_1 \) is the estimated coefficient for the factor, \( X_1 \). 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 (\( X_1X_2 \)) 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 model's prediction efficiency 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

---

**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>P6</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.
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 λ max of 276 nm, they were 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 Indian 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.

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 varying amounts of HPMC K15M and HPMC K4M alone in the outer compression coat) 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. HPMC K4M’s lack of homogeneity was responsible for the more rapid gel layer formation and higher drug release rate. Formulations with HPMC K15M (P1-P3), however, can extensively retard the drug release and form a gel more viscous than that formed with K4M and decrease drug release. Therefore, the study’s aim was to adjust the drug

<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).

Figure 2: In-vitro dissolution profile of Batches F1-F9.
release rate by combining low- and high-viscosity grades of HPMC.

**Drug release mechanism.** Both rupture and erosion mechanisms might be responsible for the time-controlled release mechanism. In-vitro dissolution profiles for all batches are shown in Figure 2. Drug release kinetics followed zero order and Higuchi- suggested controlled drug release from prepared compression coated tablets. The results of tests involving experimental batches are given in Table IV.

**Results of polynomial equations and surface response plots**

*Cumulative percentage drug release after six hours (% Q6).* The cumulative percentage drug release after 6 hrs is essential because when the dosage is administered at night, say, at 10 pm, symptoms that are experienced in the early morning hours (at approximately 4 am) 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, % Q6 was considered as one of the dependent variables in this research. The value of % Q6 varied from 2.45 to 24.16 for formulated batches and showed a good correlation coefficient (R²= 0.9148). Results from use of the polynomial equation (Equation 2) and surface plot (Figure 3) indicated that both the variables X1 and X2 showed significant effect on % Q6 (p<0.05). As the weight ratio of HPMC K15M to HPMC K4M increased, the % Q6 value decreased.

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

\[\text{Eq. 2}\]
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 and 0.9682, respectively). Results of polynomial equations (Equations 3 and 4) and surface plots (Figures 4 and 5), indicated that both the variables X1 and X2 showed significant effect on t50 and t75 (p<0.05). As the weight ratio of HPMC K15M to HPMC K4M increased, the t50 and t75 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 hours). 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 structural reorganization of hydrophilic HPMC polymer. 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. Result of analysis using a polynomial equation (Equation 5) and surface plot (Figure 7), indicated that both the variables X1 and X2 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.

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

[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 X1= -0.45 and X2=0.45. The values of X1 and X2 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 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.

Table V: Experimental responses for the checkpoint batch.

<table>
<thead>
<tr>
<th>Dependent variables</th>
<th>Observed value</th>
<th>Predicted value</th>
<th>% prediction error</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Q6</td>
<td>8.0</td>
<td>8.3</td>
<td>-3.75</td>
</tr>
<tr>
<td>t50 (hrs)</td>
<td>5.2</td>
<td>5.1</td>
<td>1.92</td>
</tr>
<tr>
<td>t75 (hrs)</td>
<td>7.2</td>
<td>7.0</td>
<td>2.77</td>
</tr>
<tr>
<td>Lag time (hrs)</td>
<td>1.4</td>
<td>1.5</td>
<td>-7.14</td>
</tr>
</tbody>
</table>

References


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Advancing Transdermal Drug Delivery

Jennifer Markarian

PATH’s Microarray Patch Center of Excellence aims to accelerate transdermal patch technology for public health needs.

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 non-profit, 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 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 program leader and Jarrahian is a program advisor, both in Medical Devices and Health Technologies at PATH.

MAP Center of Excellence
PharmTech: Please explain what the Microarray Patch Center of Excellence initiative is and how it was started. What are your current goals?

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.

Manufacturing challenges
PharmTech: What are some of the key challenges for manufacturing microneedle patches?

Zehrung and Jarrahian (PATH): 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.

Zehrung and Jarrahian (PATH): Transdermal drug delivery of –versus 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 non-profit, 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 Center of Excellence as a four-year initiative to accelerate development, particularly for global health needs, such as vaccines and essential medicines. Pharmaceutical Technology 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 program leader and Jarrahian is a program advisor, both in Medical Devices and Health Technologies at PATH.

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—program needs, product development, manufacturing, regulatory, business strategy, and engagement—that are critical to advance this promising innovation.

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) program, funded by the US 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

**PharmTech:** 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.

**PharmTech:** 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.

“MAPs could simplify storage and transport, and ultimately improve vaccine access.”

—Zehrung and Jarrahian

**PharmTech:** One of the benefits of patch delivery for vaccines is greater stability for storage and transportation, which reduces the need for a cold chain. 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.

**PharmTech:** What are some of the considerations for packaging of patches (in vaccines or otherwise)? Do you have any research projects in this area?

**Zehrung and Jarrahian (PATH):** Maintaining low moisture content over the shelf life of the product is generally critical for MAPs, as the microneedles can lose their sharpness and mechanical strength if exposed to moisture. This will require careful consideration of materials and seals for MAP packaging, and potentially incorporation of desiccant into the packaging system. In addition, it is important to consider physical protection of the microstructures if the product is dropped or crushed during storage or prior to...
Changes drive adoption of new automation models in pharmaceutical manufacturing.

During the past 10 years, new technologies have enabled data to be collected, analyzed, organized, aggregated, and made available to business needs. The adoption of the Industrial Internet of Things (IIoT) and Industry 4.0 have changed practices regarding data flow and increased the number of data sources, the type of real-time data, and the need for a centralized repository to collect, harmonize, and work on data.

In some industries such as banking, finance, retail, telecommunications and the media, systems architecture models are changing as well, leaving behind some well-known practices, such as managing business and process information with local data centers, the customization of software to local requirements, and small infrastructure networks with limited accessibility to the external world.

Against the backdrop of accelerating technology, companies need to think about how to keep their systems up-to-date, possibly with a five to ten-year view. Hardware infrastructure and software needs to be upgraded frequently, both to add functionalities and to solve bugs and vulnerabilities. All of this creates an increased need for skills to manage company systems.

In this scenario, the emerging market trend to move outside the organization systems—referred to as “XaaS” where “X” is a generic term and “aaS” is “as a service”—can provide advantages of efficiency, security, availability of best-in-class functionalities, and updated hardware.

Emerging technologies enable the main automation system vendor to offer the automation system (or part of it) as a service, using the cloud infrastructure. For example, the development and testing/validation environment can run remotely at the vendor’s cloud, while the production environment is on premises at the manufacturer’s site. This approach maximizes advantages offered by cloud solutions, such as the avoidance of hardware obsolescence and including operating systems and software infrastructure management/patching in the service, but minimizing having critical data located outside the company fences.

This article will examine how operational technology is moving towards an “as a service” model for pharmaceutical manufacturers.

XaaS defined

XaaS is a classification of information technology (IT) services in which the supplier offers a robust and cost-efficient alternative to the traditional design/procure/test/install/own/operate/retire model. Common services include:

- **Infrastructure as a service (IaaS).** IaaS provides the client access to in-house technology in servers, data storage, network infrastructure, and cyber-security, all managed and owned by third parties, which frees up capital required to secure hardware and relevant licenses.

- **Platform as a service (PaaS).** PaaS offers a remotely accessible platform that provides development and test capabilities, eliminating the need for an on-site system, which can be used to configure its own environment and applications.

- **Software as a service (SaaS).** SaaS provides access to a ready-to-use application, either running on external/remote servers or deployed locally, completely managed and maintained by service providers.

Some important differences exist between the IT world, which is the original environment where the “as a service” paradigm evolved, and the industrial operational technology (OT) landscape. The first differentiator is the...
time scale: the OT landscape tends to be in real-time, while the IT world is not bound to response time.

As shown in Figure 1, IT and OT also differ in the priorities that are the basis for defining strategies for cyber-security and deployment planning of a system. In the IT world, data confidentiality is viewed as the maximum priority in the lifecycle of a system but in the industrial OT landscape, system availability is the most important priority.

The International Society of Automation (ISA)’s ISA95 standard categorizes systems into levels (1). As shown in Figure 2, the priority of data confidentiality shifts while moving up the ISA pyramid from Level 1 (field level) to Level 5 (enterprise level) as the type of systems shift from OT to IT.

Compared to some other industries, the pharmaceutical industry has a strong regulatory framework that puts great attention on system validation and data integrity. Thus, the XaaS model to be adapted to the pharmaceutical industry in the areas of IaaS, PaaS, and SaaS.

**IaaS**

Working on the infrastructure remotely, it is now possible to design, test, and verify new network, computing, and storage capabilities before they arrive at the manufacturing site. Infrastructure can then be seen as an inner-company (i.e., within a company) “service”; remote data centers, server rooms, and network services are available today even at a geographical or wide-area-network (WAN) level with site-to-site inner-company communication. The service concept can be widely applied as something that an IT/OT infrastructure offers to the same company systems, with access to them from the same site or even other production sites through local area networks (LANs) and WANs.

The current trend is to deliver the service needed for OT architecture as an internal service, owned by the company and administrated by IT/OT company work groups. In this approach, infrastructure services such as network time protocol (NTP), back-up, anti-virus, access control, and archiving are available to any control systems and adapted to the pharmaceutical industry in the areas of IaaS, PaaS, and SaaS.
Manufacturing

device that are connected to the same network/backbone infrastructure.

Advantages of internal ownership are standardization of software products (e.g., antivirus), easier internal software lifecycle management, and better control of infrastructure services. The main disadvantage is the need to align vendors to the proposed solution; it may be necessary to move some of the vendor systems’ lifecycle management to the infrastructure owner.

Due to internal procedures to guarantee data integrity, the pharma market needs more time compared to other industries to move internal functions to third parties. The actual approach is to create virtual ambient with infrastructure services based on physical hardware, all managed by internal IT/OT. Once this transition is completed and consolidated, the use of IaaS from third parties should be simple and easy to manage.

PaaS

A good example of PaaS delivery in the pharmaceutical industry is the process control system engineering environment. Increasingly, remote development suites are available from process control system vendors, which allows for remote accessibility and sharing of engineering data and databases with different development groups.

Following the “intra-company” approach, PaaS provides testing and simulation capabilities across corporate sites, and the same environment can be developed, maintained and used by different teams. Further, the availability of a separate system environment for developing, testing (validation), and simulation (training) that does not have any impact on production can have benefits in terms of productivity and efficiency.

The benefits of using the PaaS approach include the easy availability of remote access to control systems from different locations and the ownership of one environment across different sites and corporate locations. A potential challenge is the necessity for a good level of control system standardization across different production plants and sites. Pharma companies may have control systems from different suppliers. Once the suppliers of these control systems use the available PaaS, pharma companies can also move in the same direction.

SaaS

Data history and analytics, reporting, and label management are available as software services. SaaS can be seen as service on the cloud, where it is supplied by external software houses and providers of data analytical services and intra-company services (e.g., data historians). Data integrity and confidentiality are even more important in SaaS than in IaaS and PaaS.

The benefits of SaaS for pharmaceutical manufacturers include that the services are delivered by large software players with advanced technologies. These systems often require large amounts of calculation power, large databases, and the continuous upgrade of algorithms; with SaaS these concerns are the responsibility of the provider rather than the manufacturer.

Data integrity and confidentiality are even more important in SaaS than in IaaS and PaaS.

The disadvantage of SaaS for pharma manufacturers is that these systems typically require restricted, confidential data access to maintain data integrity. SaaS can thus be seen as a risky practice. The general pharma industry culture uses the model of local segregated data storages owned and physically secured by the data owner. The authors expect, over the next years, to see an upgrading of cybersecurity and privacy concepts to increase safety levels. In parallel, service providers will develop specific tools for the pharma market to guarantee the data integrity and confidentiality needed for this market.

Advantages of XaaS in pharma

Pharmaceutical manufacturers can benefit from applying the concept of service not only to cloud solutions but also to intra-company services. IT/OT competencies can be centralized in a highly specialized team, delivering infrastructure services widely across the company. Centralizing data centers and servers may result in space optimization. Availability of development platforms as a service avoids ownership effort of such systems, while providing advantages in the availability of different environments for developing, testing, and simulation/training. At the application level, sophisticated software tools, which may be onerous to own from both a calculation power and financial standpoint, can be accessed as a service.

Reference

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Quality/Regulations

Evaluating the Tech Transfer Process
Susan Haigney

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

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 spoke with Zimmermann about the tech transfer process and how companies can make this transfer as painless as possible.

Beginning the tech transfer process
PharmTech: 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, 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.

PharmTech: 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!

PharmTech: 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
PharmTech: 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.

PharmTech: 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 possi-
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.

PharmTech: 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.

PharmTech: 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).

Next steps
PharmTech: What are the next steps for the Center of Excellence initiative?

Zehring 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.
Although therapeutic creams and ointments have been in use for centuries, development of topical pharmaceuticals is complex and costly. Many 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 FDA, pointed out in 2017 (1).

But individual patient differences 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 topicals. “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 July 30, 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: in order to be similar, the generic and reference drug would not only have the same components but they’d follow the same exact recipe and composition. Q3 similarity 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 "thermo-dynamically 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’s (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 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 most far-reaching was its draft guidance for determining the bioequivalence for acyclovir cream, published in 2016 (4), which spelled out clearly how in-vitro release and in-vitro penetration study data might be used to enable the issuance of a biowaiver. In this case, a developer could skip clinical bioequivalence testing if both test and reference drugs showed Q1, Q2, and Q3 similarity; they both showed an equivalent rate of API release based on IVRT testing; and they were shown to be bioequivalent based on acceptable IVPT results.

FDA is clearly stepping up its efforts to facilitate development of topical generics. To date, 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 that were issued by FDA’s Office of Generics, and minor revisions were planned for another 53 topical product-specific guidance documents, 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, July 30 2019.
Developments in the Pharmaceutical Outsourcing Industry

Susan Haigney

Contract manufacturers are making strategic partnerships and expanding services in the last quarter of 2019.

The burgeoning cell therapy and gene therapy market segments continue to spur new partnerships and business expansions for contract manufacturing organizations (CMOs) and contract development and manufacturing organizations (CDMOs) in the second half of 2019.

CombiGene, a gene therapy company located in Sweden, announced it signed an agreement with Cobra Biologics—a CDMO that provides DNA, viral vectors, and microbiota for preclinical, clinical, and commercial supply—for the production of the epilepsy gene therapy candidate drug CG01 (1).

The agreement includes a Master Service Agreement that details the terms under which the two companies will collaborate. There will be three separate contracts: quality, production of plasmids, and production of CG01. The agreement includes manufacturing of CG01 by Cobra for clinical studies and future commercial production, according to a company press release.

In October 2019, Lonza announced an extension to its partnership with Genmab, a Denmark-based biotechnology company specializing in antibody therapeutics for cancer, which covers preclinical and clinical development and manufacturing for part of Genmab’s pipeline (2). Lonza’s Ibex Solutions in Visp, Switzerland can be used for Genmab to take their candidates from gene to investigational new drug application in 12 months and move to reserved manufacturing capacity in Ibex Develop for clinical manufacturing and biologics license application submission. The new agreement will cover development and clinical manufacturing of drug substance and drug product for certain programs in Genmab’s pre-clinical and clinical pipeline.

Lonza also announced it is entering into a manufacturing service agreement with Cellectis, a clinical-stage biopharmaceutical company that specializes in developing immunotherapies based on allogeneic gene-edited chimeric antigen receptor (CAR) T cells (UCART), for the clinical manufacturing of Cellectis’ allogeneic UCART product candidates targeting hematological malignancies (3).

Manufacturing of the cell line will take place at Lonza’s GMP facility in Geleen, Netherlands where the frozen, off-the-shelf, non-alloreactive engineered CAR T cells will be industrialized with defined pharmaceutical release criteria for the patient population.

Commercial supply agreement
Catalent announced it has entered into a long-term commercial supply agreement with Minerva Neurosciences, a Waltham, MA-based biopharmaceutical company focused on the development of therapies to treat central nervous system disorders (4). The companies will focus on rolupereidone (MIN-101), an investigational compound under development by Minerva, for the treatment of negative symptoms of schizophrenia.

A Phase III clinical trial is currently being conducted in Europe and the United States, according to a Sept. 24, 2019 press release. If successful, rolupereidone (MIN-101) will be the first treatment approved to treat symptoms of schizophrenia in the US, according to the companies.

References
Sartorius Acquires Danaher Life Science Businesses for $750 million

Sartorius announced on Oct. 21, 2019 it has signed an agreement to acquire parts of Danaher’s Life Science Portfolio for $750 million in cash.

According to a press release, the agreement highlights three businesses that are part of the Washington, DC-based science and technology company Danaher Life Science’s portfolio. The businesses include:

• FortéBio, a label-free biomolecular characterization business that houses protein analysis instruments, biosensors, and reagents for drug discovery, located in Fremont, California and Shanghai, China.
• The Bioprocess Solutions division, which is comprised of multi-use and single-use equipment and chromatography columns and resins, located in Europe and the United States.
• SoloHill, a company that uses microcarrier technology and particle validation standards used in cell culture and other bioprocesses, located in Ann Arbor, MI.

Sartorius plans to expand sectors of its business to fit the acquired companies, according to the release.

The transaction is set to be completed in the first quarter of 2020.


Takeda Acquires Global License for Celiac Disease Therapy for $420 million

Takeda Pharmaceutical announced it acquired a global license to develop and commercialize the investigational medicine CNP-101/TAK-101, an immune modifying nanoparticle containing gliadin proteins for the treatment of celiac disease, from Cour Pharmaceutical Development Company, a therapy development company headquartered in Northbrook, IL, for $420 million.

According to a press release, the therapy received positive results in a randomized, double-blind, placebo-controlled clinical trial in 34 adults with proven celiac disease. Based on the results, Takeda decided to move forward with a dose-ranging study that explores the potential of TAK-101 in the treatment of patients with celiac disease on a gluten-free diet to inform future registrational trials.

“We are encouraged by the data from this first human proof of concept study of our proprietary nanoparticle platform designed to reprogram the immune system,” said John J. Puisis, CEO of Cour Pharmaceuticals, in the press release.

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 authorized 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


Table I: Example review responsibilities matrix.

<table>
<thead>
<tr>
<th>User/operator</th>
<th>Functional manager</th>
<th>Quality unit</th>
<th>Regulatory affairs</th>
<th>Health and safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Technical review</td>
<td>-Functional correctness review</td>
<td>-Compliance with the regulations review</td>
<td>-Compliance with the marketing authorization review</td>
<td>-Compliance with applicable regulations and company rules</td>
</tr>
<tr>
<td>-Functional correctness review</td>
<td>-Quality of information/text review</td>
<td>-Compliance with the quality system review</td>
<td>-Format/layout review</td>
<td></td>
</tr>
</tbody>
</table>

Your opinion matters.

Have a common regulatory or compliance question? Send it to shaigney@mmhgroup.com, and it may appear in a future column.
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