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Erika Riehle
Sr. Clinical Supply Chain Manager, Fisher Clinical Services
Thermo Fisher Scientific
The Key Word: Quality

Bio/pharma companies cannot spell success without solving all elements of quality programs.

T
he end of the year is the traditional time to assess achievements and shortfalls of the past 12 months. A preliminary review of the bio/pharma industry accomplishments shows some impressive results. By the end of November 2018, FDA had approved 53 novel drugs, setting a pace for the most approvals on record.

The approvals included notable advances in science and targeted medicine. On November 26, FDA approved Vitrakvi (iarotrectinib), the second cancer treatment approved based on a biomarker for different types of tumors rather than tumors originating in a specific organ or part of the body. The therapy is the first to receive a tumor-agnostic indication at the time of initial FDA approval (1).

In announcing the approval, FDA Commissioner Scott Gottlieb noted that the therapy marked “a new paradigm in the development of cancer drugs that are ‘tissue agnostic.’” Gottlieb also credited increased knowledge of cancer mutations, breakthrough therapy designation and accelerated approval processes, and a modern framework of clinical trial designs as contributing to more targeted and effective cancer treatments.

Quality across and down
While the approvals marked progress in innovation, the global recall of the API valsartan due to the discovery of impurities N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) in drug products raised questions about the quality of drug substances in the supply chain.

Innovation, science, and a dedication to quality help define pharma success.

Quality problems were a mixed bag this year. The number of warning letters issued by FDA were on a slightly slower pace compared with 2017; however, the number of drug recalls were up.

While innovative achievements such as new drug approvals get the headlines and are recognized and rewarded, quality programs are essential but rarely get the attention until something goes wrong. In this issue, and in supplemental online coverage, the editors present multiple views of quality issues throughout the drug development and manufacturing continuum.

In this issue
Analytical quality by design: Representatives from global bio/pharma answer key questions about an enhanced approach to the lifecycle of an analytical procedure based on practical experience of applying these concepts to real projects.

Validating supplier quality: Consultants and experts in risk assessment share best practices that will help ensure the quality of APIs, ingredients, and process aids and materials.

Technology transfer: The handoff from inventor to contract development and manufacturing organization partner, depends on communicating the right information at the right time. This article examines recent failures and lessons learned.

Standard operating procedures: FDA warning letters often refer to training deficiencies. Learn the underlying technical and cultural reasons and why it can be difficult to tie employee training programs to business objectives.

Risk assessment and mitigation: Learn how non-compliance can exacerbate drug shortages and how it can play into affordable healthcare.

Online quality resources
The editors regularly add features, news, and reports on a range of quality issues to the PharmTech website. Recent additions include mock inspections, eliminating obsolete heavy metals test, and lot release testing. Bookmark www.pharmtech.com/quality for quick access to the latest bio/pharma quality topics.

Reference
1. FDA, “FDA Approves an Oncology Drug That Targets a Key Genetic Driver of Cancer, Rather Than a Specific Type of Tumor,” Press Release, Nov. 26, 2018. P T
Sterile, Integrated Hood and Mask

Kimberly-Clark Professional added the Kimtech AS Sterile Integrated Hood and Mask XL for head shapes, sizes, and hairstyles that pose a challenge to standard aseptic gowning for cleanroom operators.

The new gowning size combines two donning steps (hood and mask) into one, simplifying the donning process and further reducing the risk of contamination. This sterile product features a stretch-fit elastic hood and opening, tunneled overseams to prevent particle shedding, and Clean-Don Technology ties for a more secure fit. Additionally, the company says it provides free fittings.

Kimberly-Clark Professional
www.kcprofessional.com

Robotic System Loads Trays for Prefilled Syringes

ESS Technologies has developed a robotic tray loading system that gently handles glass prefilled syringes. The high-speed pick-and-place system integrates three FANUC LR Mate 200iD robots with ESS-designed end-of-arm tooling (EOAT) to automate loading five-count thermoformed trays at a rate of up to 25 trays per minute.

The operator manually loads thermoformed trays into high-capacity tray magazines. Syringes enter the starwheel infeed via an infeed track that connects to the syringe-filling equipment at a rate of 125 syringes per minute. A starwheel picks syringes and lays them in carriers on the infeed conveyor. The first FANUC robot uses vacuum EOAT to pick a tray and, with the help of line tracking, places it on the lugger tray transport conveyor. A second robot, also equipped with line tracking, picks five syringes from the syringe infeed conveyor, loads three in the tray, and rotates the remaining two syringes 180-degrees before placing them to complete the tray. Any missed syringes fall into a soft discharge bin to be manually re-introduced into the robotic tray-loading cell.

Loaded trays convey to a tamping station that gently presses all five syringes into their locking cavities. At the discharge, a third FANUC robot uses a hybrid vacuum/gripper EOAT to rotate a tray and stack it on the tray that follows. The robot then picks both trays and places them on a discharge conveyor for downstream inspection and cartoning.

ESS Technologies
www.esstechnologies.com

150-Gallon Double Planetary Mixers

Charles Ross & Son Company recently developed two specialty customized 150-gallon double planetary mixers (Model DPM-150) with patented high viscosity blades. Features include interchangeable jacketed vessels, electrohydraulic lift, recipe controls with data logger, and an all stainless-steel sanitary design. The mixers consist of two identical blades that move in a planetary motion, rotating on their own axes as they orbit a common axis. In 36 revolutions around the vessel, the two blades pass through every point in the product zone, physically contacting the entire batch. When mixing high viscosity products upwards of two million centipoise, the blades impart a kneading action to the batch, smoothing out its consistency and breaking up any agglomerates.

Ross, Charles & Son
www.mixers.com

Mobile App for Supply-Chain Traceability

DispaX is a mobile application from Adents developed for pharmaceutical warehouses, wholesalers, distributors, and dispensers such as pharmacies and hospitals for improved supply-chain traceability.

The solution offers three ways to search data: scanning a label, entering a serial or delivery number, or entering a lot number. The application enables users to query by lot, delivery number, serial number, and levels up and down the hierarchy tree. Features include the ability to see all details of an item, navigate up and down parent-child aggregation relationships, manage the products picking, and view shipment history.

Adents
www.adents.com
Quality Manufacturing Key to Reducing Drug Shortages

Jill Wechsler

Despite ongoing efforts to address drug shortages, FDA reports a rise in active shortages and in the duration of supply problems.

Patients, providers, and policy makers are up in arms over persistent and more prevalent shortages of important medicines, primarily generic sterile injectables needed to treat critical diseases and infections, provide emergency care, and enable surgery and multiple aspects of medical care. Despite ongoing efforts to address the problem, FDA sees a rise in active shortages and in the duration of supply problems, according to data presented at a public meeting on drug shortages in late November 2018, sponsored by FDA and the Duke Margolis Center for Health Policy (1). Some shortages have lasted more than eight years, and solutions remain elusive.

Stakeholders participating in the FDA public meeting looked to address the systemic root causes of shortages, with a focus on the economic incentives likely to drive product quality, supply chain resiliency, and appropriate reimbursement for drugs. In some cases, said FDA Commissioner Scott Gottlieb, “the prices reimbursed on these drugs have been driven down to such low levels, that it makes it hard to manufacture them profitably and have enough margin left over to invest in modern manufacturing upgrades” (2).

FDA continues to urge industry to adopt more reliable, high-quality manufacturing systems.

Adam Kroetsch, deputy director of the Office of Program and Strategic Analysis in the Center for Drug Evaluation and Research (CDER), linked shortages to older generic drugs where the market fails to reward product quality and reliability.

Consolidation throughout the supply chain was cited as a key factor in aggravating shortages. Mergers in the generic-drug industry can limit production of a drug to one firm and minimize sources of key ingredients. A handful of hospital buying groups and large distributors, moreover, limit competitive bidding opportunities and overall reimbursement for common, but important, injectables.

Seeking new solutions

A full range of issues and proposals will be weighed by an FDA Drug Shortages Task Force, formed in July 2018 in response to rising concerns from members of Congress (3). The panel includes representatives from the Centers for Medicare and Medicaid Services, the Federal Trade Commission, and other federal agencies, as well as senior leaders from FDA. The group has been meeting with manufacturers and other stakeholders leading up to the public meeting with the goal of developing a report to Congress outlining a policy framework to resolve the problems underlying persistent drug shortages.

Manufacturers at the meeting cited unclear or changing FDA product development standards and noted that efforts to scale up production to address a shortage can be stymied by FDA’s complex post-approval changes requirements. Several speakers urged greater transparency in agency warning letters and inspection reports to provide information earlier on where quality problems at one manufacturer may lead to limited production and create an opening for added competition. To avoid delays in gaining FDA approval of new or upgraded facilities to produce alternative products, the agency noted its adoption of a more efficient inspection program for sterile drug facilities, with more transparent quality standards that will make the oversight process more predictable.

There was disagreement among participants on some issues, with certain manufacturers seeking incentives to produce drug components in the United States to shorten supply chains, while others maintained that high-quality products can be obtained reliably overseas. Generic-drug makers urged flexibility in meeting product standards that FDA revises after drug
development and testing is underway. David Gaugh of the Association for Accessible Medicines (AAM) proposed federal grants or other assistance to help manufacturers upgrade or build new manufacturing facilities to provide excess capacity for when shortages occur and to establish a national contingency plan to stockpile critical medicines (4).

FDA officials continue to urge industry to adopt more reliable, high-quality manufacturing systems to avoid production breakdowns, but gains have been elusive. A CDER quality metrics initiative has been mired in dispute for months over what and how to measure quality operations and a firm’s “quality culture.” CDER’s emerging technology program offers advice and support to companies looking to adopt continuous manufacturing and other advanced production technologies, but uptake has been limited. Efforts to streamline the post-approval changes process also have fallen short in modifying agency oversight of manufacturing revisions. At the same time, newer just-in-time manufacturing systems that reduce vendor inventories may increase vulnerability to unexpected shortages. All these issues are before the FDA taskforce and will be considered in its report on the multiple challenges for all supply chain parties in preventing drug shortages to ensure public health.

A full range of issues and proposals will be weighed by an FDA Drug Shortages Task Force.

References
As niched global markets grow and increase the complexity of pharmaceutical manufacturing, vendor management has become more challenging; the API and excipient supplier base has moved offshore, and more core operations are being outsourced to contract partners. Today, a typical pharmaceutical manufacturer works with 100–200 contract manufacturing organizations (CMOs) (1). A 2013 study found that supply and supplier issues account for 40% of the pharmaceutical industry’s top supply-chain risks (2).

Adding to the difficulty have been corporate mergers and acquisitions, both on the manufacturer and on the supplier sides. Mergers shift the focus away from manufacturing, as Steve Cottrell, president of Maetrics, wrote in April 2018 in the PharmaPhorum blog (3). This, in turn, limits “the ease with which supply chain gap analyses, supplier assessments, and quality assurance checks (e.g., non-conformance or out-of-stock issues) can be carried out,” he wrote.

The results have been clearly seen in an increase in drug shortages, recalls, and regulatory citations for insufficient quality management and vendor oversight. Overall, supply reliability issues cost biopharmaceutical companies $2 billion in revenue each year, according to the Boston Consulting Group (4). Pharmaceutical manufacturers still have limited visibility into their supply chains, and fairly loose, ad hoc connections with many of their vendors, in sharp contrast to the close supplier-manufacturer partnerships and data exchange programs that exist in the automotive, aerospace, and electronics industries.

**Industry efforts**

Manufacturers have been working individually and in concert to address these issues, through initiatives such as the Pharmaceutical Supply Chain Initiative (PSCI), a group of 33 manufacturers that has developed best practices, self-assessment guidelines, and an audit protocol based on the principles of sustainable sourcing and traceability, transparency, business resilience, and management capability and systems.

The organization, which started up in 2005 with five members, has trained 190 auditors and 150 staffers at pharmaceutical industry suppliers in best practices and principles and is promoting the concept of shared supplier audits to reduce costs for manufacturers and their suppliers. The number of shared PSCI audits more than doubled from 61 in 2016 to 152 in 2017, according to Enric Bosch Radó, a manager in Boehringer-Ingelheim’s environmental health and safety department, who presented a progress report at Salon International de la Logistique (SIL), the international logistics meeting in Barcelona on June 5, 2018 (5).

**Real-time data exchange and trust**

BioPhorum, a collaborative industry effort, is working on a blueprint for 21st century supply chain management as part of its Technology Roadmap program. Newer technologies, such as single-use systems for cell culture, Protein A, and chromatographic resins, require a significant investment from biopharmaceutical manufacturers, according to the group’s latest report (6), while the cost of poor quality (evident in raw material variability and lack of understanding and control of the supply chain) is high and must be driven out. Close collaboration between manufacturers and vendors will be increasingly important for ensuring supplies of single-use technologies, and as more companies evaluate continuous bioprocessing, said Jonathan Haigh, head of downstream processing at FujiFilm Diosynth, a company that is both a manu-
The group is also working on improving workshop addressing challenges in the use include supply chain business continuity planning and forecasting and planning software. BioPhorum has called for change management, interacting, and to promote harmonized practices using electronic data exchange. Roche avoids being dependent on overseas suppliers.

Sharing best practices
One method that suppliers and their customers are using to attempt to balance rapid growth in demand and the need for careful planning is the sales and operational planning process, which examines inventory replenishment and distribution needs, and assesses manufacturing, including manufacturing and quality equipment and warehousing and how well it can support customer requirements, said Aida Tsouroukdissian, head of demand planning at MilliporeSigma in a 2018 video (8). Other methods being used include supply chain business continuity planning and supply chain mapping as well as change management.

There is a need to go beyond the superficial level, noted Roger Estrella, senior risk manager for supplier business continuity at Genentech, in an Rx-360 workshop addressing challenges in the pharmaceutical raw material supplier chain (9). Estrella’s business continuity group works closely with Roche’s corporate quality risk organization, which handles audits, recalls and customer complaints, and process capability to be able to respond to and find the root cause of quality issues. Roche analyzes suppliers based on their potential impact on the business and the patient. The first question is what would happen to patients if there were a problem with the supply of this particular product? What impact would a supply disruption have on revenues and on patients? Materials are classified based on level of risk (e.g., oncology products would be placed in a higher category of risk than treatments for rheumatology), he said.

Manufacturers must identify hazardous conditions, assess risks and develop contingency plans, get them approved and then implement them. Challenges to asserting full control over supply chains include cognitive bias, supply chain complexity, and business change management, Estrella said. Too often, employees may tend to discount risks, especially those that may occur in the future, he said, adding that strengthening supplier risk assessment requires a top-down approach and senior-level management support if it is to succeed. He said that, wherever possible, Roche avoids being dependent on overseas suppliers.

Going beyond the surface
It is no longer enough for manufacturers to have transparency from most important suppliers; they now need insights into how these suppliers manage their supply chains, Estrella said. Roche asks that suppliers give them some idea of their business continuity management by conducting manufacturing risk assessments at each relevant manufacturing site; developing mitigation plans for each risk; determining worst-case scenarios for the most likely site risks; and estimating the time that it would take for them to return to normal after a supply upset. If suppliers aren’t already doing this, the company helps them with the process and uses results to develop its risk mitigation inventory levels for the particular material, he said.

Manufacturers must also look at each supplier’s business portfolio and ask how each particular product fits into that vendor’s big picture. “Consolidations have complicated the supplier-manufacturer picture. Every time that a merger and acquisition takes place, a rising star product can become a dog, and the new owners may decide not to invest in quality and delivery performance initiatives,” he said. In some cases, the new business owners may even stop making a product that has always been important to the manufacturer’s business, and biopharmaceutical manufacturers must be prepared and develop alternatives. He also noted that a supplier may be critical to an individual biopharmaceutical company’s business, yet biopharmaceutical manufacturing may not be a major market focus for them, so manufacturers should be prepared. In general, he said, manufacturers must know suppliers, and must work to minimize the number of intermediates in the supply chain. “The more handoffs you have, the more potential points of failure,” he said. So if there are handoffs it is essential for manufacturers to know who is involved and how they will handle any situations that may come up.

Stressing the importance of supply chain mapping and risk management, he noted that it is straightforward to identify risk, but challenging to mitigate it. Biopharmaceutical manufacturers must be prepared to understand and communicate more closely with suppliers to prevent quality and supply problems from affecting patients and their bottom line.

References
In 2010, the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Pharmaceutical Research and Manufacturers of America (PhRMA) groups focusing on analytical quality by design (QbD) published a joint paper to stimulate industry discussion and debate around the implications and opportunities of applying QbD principles to analytical measurements (1). This topic is now commonly referred to as an ‘enhanced approach for development and utilization of analytical procedures’.

In this article, the terms ‘analytical procedure’ and ‘analytical method’ are used interchangeably. Since this publication, industry, regulators, and pharmacopeias have debated the concepts widely and, as with any new paradigm, the concepts have evolved considerably. Additionally, new regulatory concepts have been developed to support pharmaceutical product lifecycle management.

While the technical benefits of applying an enhanced approach to the lifecycle of an analytical procedure are clear, it can be helpful to describe how to apply the concepts and tools to show how these benefits can be realized. The purpose of this article is to propose definitions, exemplify the use of individual elements of this enhanced analytical lifecycle concept, and to identify areas where they could help to support emerging regulatory concepts and/or guidance.

What is the enhanced approach?
The lifecycle of an analytical procedure is generally understood to encompass all activities from development through validation, transfer, operational execution, and change control until final discontinuation. Application of the enhanced approach for the development and use of analytical procedures within the analytical lifecycle management concept aligns with one of the key quality risk management principles outlined in International Council for Harmonization (ICH) Q9: “The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient” (2).

The enhanced approach for analytical procedure lifecycle management focuses development effort on understanding sources of variability and controlling parameters that truly affect the output from the analytical procedure (i.e., the reportable result).
This will result in more robust and rugged analytical procedures that are controlled, within predetermined operational parameter range(s) and/or region(s) so that they consistently deliver the output within predefined target performance criteria.

The enhanced approach uses science and risk-based approaches that build on the concepts and tools described in ICH Q8 (3), Q9, Q10 (4), and Q11 (5), and certain associated process validation guidelines (6). It then applies these approaches to gain enhanced understanding of the analytical procedure through its lifecycle (see Figure 1 for an overview of the enhanced approach).

The analytical controls for a pharmaceutical product comprises specifications—tests, references to procedures, and acceptance criteria—as described in ICH Q6A and B (7,8). Acceptance criteria are usually linked to defined quality attributes. In the enhanced approach, the measurement requirements for each quality attribute are defined in an analytical target profile (ATP), which can be used as a tool to aid analytical procedure development, qualification, verification, and continued improvement.

The ATP for a measurement performs a similar role to the quality target product profile (QTPP) defined in ICH Q8 for a pharmaceutical product. Compendial and regulatory requirements, or consensus industry guidance, that include acceptance limits or ranges for specific quality attributes will aid understanding of accuracy and precision requirements and can therefore contribute to building the ATP (9).

Once defined, the ATP can be used as follows:

- To direct the selection of an appropriate analytical technique.
- To support risk assessment and rigorous systematic evaluation of procedure variables. The ATP is used to develop a full understanding of how input parameters affect the reportable result leading to development of an analytical procedure.
- To serve as the focal point for continuous improvement and change control of the analytical procedure within the analytical lifecycle management concept.

Enhanced understanding enables the definition of conditions (parameter set points and/or ranges) that provide a high degree of confidence that the procedure will consistently generate results that meet the requirements of the ATP. If procedure parameter ranges are determined and evaluated, these are referred to as a method operable design region (MODR).

The MODR is analogous to the design space concept applied to products and processes introduced in ICH Q8 and has been described (1) and exemplified extensively elsewhere (10–12). Univariate and/or multivariate experimental design approaches may be de-
ployed to establish a MODR, so that an in-depth understanding of the interactions and criticality of procedure parameters, with respect to their impact on specific performance criteria, and the reportable result, can be achieved. The MODR constitutes a region within which changes can be made without impact on the reportable result, and therefore, its boundaries should not be close to any identified edges of failure.

The enhanced approach features a systematic assessment of inputs and how they impact robustness and ruggedness (13) of the procedure; this facilitates the definition and establishment of controls within the analytical procedure that ensure consistent operation. ICH Q8 defines the control strategy as a planned set of controls, derived from current product and process understanding, which ensures process performance and product quality.

In an analogous fashion, an analytical procedure could contain the following key elements:

- A system suitability test (SST) as described in ICH Q2 R1 (14) and the pharmacopeias. For an analytical procedure developed using the enhanced approach, the SST limits should ensure that the ATP criteria are consistently met and all parameters critical to procedure performance are appropriately controlled. SST criteria are traditionally selected to confirm measurement system performance prior to and/or during analysis and may include resolution, injection precision (for chromatographic methods), detection limit, linearity criteria, or reporting limits. Additional controls that verify the performance of the constituent operational units within a procedure (such as variability of standard or sample preparation, resolution of critical components, extraction efficiency, and analysis of control samples), and therefore act as additional confirmation of procedure performance, may further support the ATP as part of a performance-based approach to procedure change control.

- A detailed set of instructions that clearly specify parameters requiring control identified during risk assessment, development or validation (robustness) experiments. This may be a range or set point, or combination of both. These instructions allow the trained analyst to operate the procedure correctly and thus meet the criteria described in the ATP.

- A defined replication strategy (e.g., the number of injections and sample preparations) that define the reportable result. By increasing the number of replications, the precision of the mean can be improved, as required by the ATP (15).

- A quality system that supports an enhanced approach including written standard operating procedures, change management and facilities/equipment operation, control forms, and continual monitoring performance criteria.

- Continual monitoring of critical predefined criteria to identify when changes or adaptations are necessary during the analytical procedure lifecycle. The increased understanding that the enhanced approach delivers, aids in identifying the implications of any proposed change and informs any change assessment strategy.

As a pharmaceutical product progresses through the development lifecycle, the associated ATPs for each of the measured quality attributes should be refined as needed to ensure the associated procedures fully support the evolving clinical and commercial specifications. If performance requirements or specifications change, ATPs can be revised accordingly, and the suitability of the methods re-assessed (if required). Examples of the performance criteria that could potentially be included in an ATP for three different types of measurement are provided in the online version of this article. Further exemplifications of ATPs can be found in the literature (16,17).

The benefits of applying the enhanced approach on validation and transfer

The enhanced approach for the development and application of analytical procedures uses risk assessment and systematic experimental evaluation to gain enhanced understanding of the procedure parameters critical to the consistent delivery of fit-for-purpose reportable results.

Such enhanced understanding leads to the development of analytical procedures whose performance criteria are based on the requirements of the reportable result throughout the analytical procedure lifecycle. This understanding further underpins knowledge of the impact to procedure performance when individual or combined critical inputs are changed. Consequently, there is increased understanding (and control) of the inherent variability associated with the reportable result through the procedure lifecycle, which ultimately facilitates greater understanding of true process variability.

Furthermore, the enhanced operational robustness of analytical procedures strengthens the continuity of the supply chain by lowering the risk of procedure related problems and by enabling more efficient, robust out-of-specification and out-of-trend (OOS/OOT) investigations and root cause determination if problems are observed.

In an enhanced approach, performance qualification and verification are part of the lifecycle—the demonstration of an analytical procedure’s suitability is not a singular activity, but instead part of continued assurance that it remains fit-for-purpose throughout its deployment. This includes when any changes are made to the procedure parameters or its operating environment.

The analytical procedure lifecycle approach is aligned with the three sequential stages described in current process validation guidelines: procedure design (stage 1), procedure performance qualification (stage 2), and continued performance verification of the procedure (stage 3). An
analytical procedure that is designed in stage 1 is qualified against the performance acceptance criteria derived from the ATP at stage 2 (analogous to a traditional method validation and transfer into a receiving site). During stage 3 (routine application) monitoring of critical performance attributes ensures the procedure continues to meet the requirements of the ATP.

If changes are made to the analytical procedure that impact the quality of the data produced, a further qualification exercise should be performed to confirm the procedure performance continues to meet the requirements of the ATP. Performance monitoring across the lifecycle, change management, and efficient knowledge transfer are facilitated by well-designed analytical controls that ensure the procedure delivers fit-for-purpose data throughout its lifecycle.

In summary, the benefits of the enhanced approach include reliable analytical procedures with performance criteria based on the requirements of the reportable result. Furthermore, these analytical procedures have less likelihood of ‘failure’ (which can better ensure product supply), lend themselves to more efficient investigations if OOS/OOT results are observed, and come with knowledge and understanding about how procedure performance is impacted when both individual and combined critical inputs are changed.

The traditional versus the enhanced approach
The traditional approach is typically an iterative and univariate process with emphasis on meeting predefined, and often generic, validation criteria and limited use of risk assessment and structured experimental design. The enhanced development approach fundamentally differs in its dual recognition of the need to i) systematically identify and understand the interconnected multivariate procedure parameters which have potential to influence the performance of the analytical procedure and ii) evaluate quality risks posed by these parameters based on their impact on the reportable result.

This holistic understanding facilitates lifecycle activities such as the transfer and improvement of analytical procedures and support to any investigations required by providing a common knowledge base and baseline for procedure performance. For traditionally developed methods, these activities are often performed independently, with redundancies and duplication, leading to less efficient change management.

An ATP could also be developed and applied retrospectively to a traditionally developed analytical procedure for the purposes of continual monitoring and improvement, if considered appropriate. For example, as a result of investigations on OOS/OOT results or, for a post-approval tightening of a specification limit it may be helpful to revisit or even define the required analytical performance for the first time. In the enhanced approach, the ATP is prospective and serves as focal point for the continuous improvement of the analytical procedure.

Suitability of the enhanced approach
The principles of the enhanced approach can be applied to any type of analytical technology and are not restricted to specific molecule classes or method types (e.g., the approach is applicable to in-line or at-line, as well as off-line analyses). The greatest value is gained from the application of the enhanced approach to measurements that present a significant risk of variation or inconsistency as a result of the complexity of the measurement or the nature of the analyte. Simple methods such as those resulting in a qualitative result, or simple pharmacopeial tests and limit tests, are less likely to benefit from adopting an enhanced approach.

Supporting processes and practices
Sound knowledge management and quality risk management is recognized as an important enabler of the enhanced approach for development and application of analytical procedures. A company’s quality system should support the design, qualification/validation, and continued verification and improvement stages for analytical procedures.

Suitable processes or business practice may include how to generate an ATP, how to perform a risk analysis and define the analytical controls for analytical procedures, qualification/verification of analytical procedures and handling non-conformances with acceptance criteria predefined in qualification protocols and the ATP, internal and regulatory change control of analytical procedures and exchange-ability of alternative procedures, and how to monitor and trend analytical procedure performance in a continued manner as well as handling unfavorable trends.

Current progress
An overall lifecycle concept for analytical procedures, including ATP definition and use as a development tool, has been described in a series of stimuli articles by expert working groups in the United States Pharmacopeia (USP) (18–20).

A number of papers dating back to 2007 have considered how application of enhanced tools can be applied during the analytical procedure lifecycle, with particular focus on chromatographic technology platforms (21). These papers have cited the specific elements of the enhanced approach and outlined how statistical experimental design and handling of the data, risk assessment, categorization, and prioritization tools can all lead to greater understanding and controls to assure the requirements for the reportable result.

A Parenteral Drug Association (PDA) workshop on the role of the analytical scientist in QbD recognized the challenges of harmonizing new approaches across multiple stakeholders as a result of the global nature of the pharmaceutical industry (22). Similarly, two USP workshops on the
lifecycle approach to validation of analytical procedures have explored the statistical tools and provided examples of their application (23, 24).

A more recent industry survey posed several questions about progress with analytical quality by design. Approximately half of the companies polled were implementing some aspects of the enhanced approach. The survey concluded that while the benefits are clear in terms of the development of more robust procedures, the desired streamlining of regulatory aspects of analytical procedure change processes have not been realized so far (25).

**Future opportunities**

At the time of writing, the ICH Q12 Product Lifecycle Management guideline has reached Step 2 in the ICH process (26), with publication of the draft guideline (27) and requests for comment in a number of regions. The guideline may therefore undergo revision before it finalized at Step 4 and then implemented in the ICH regions at step 5 in the ICH process. The Q12 guideline: “provides a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner. It is also intended to demonstrate how increased product and process knowledge can contribute to a reduction in the number of regulatory submissions. Effective implementation of the tools and enablers described in this guideline should enhance industry’s ability to manage many CMC changes effectively under the firm’s Pharmaceutical Quality System (PQS) with less need for extensive regulatory oversight prior to implementation.”

The Q12 Step 2 document includes a number of concepts/tools that may be relevant to analytical lifecycle management within the following chapters:

- Chapter 3: Established Conditions (ECs)
- Chapter 4: Post-Approval Change Management Protocols (PACMPs)
- Chapter 8: Structured Approach to Analytical Procedure Changes

Established Conditions are defined in Chapter 3 as follows:

“ECs are legally binding information (or approved matters) considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority.”

Within Chapter 3, there is a description of how to identify ECs for analytical procedures and a caution that the extent of ECs could vary depending on the method complexity, development, and control approaches. Two control approaches are noted:

- “Where the relationship between method parameters and method performance has not been fully studied at the time of submission, ECs will incorporate the details of operational parameters including system suitability.”
- “When there is an increased understanding of the relationship between method parameters and method performance defined by a systematic development approach including robustness studies, ECs are focused on method-specific performance criteria (e.g., specificity, accuracy, precision) rather than a detailed description of the analytical procedure”.

It is important to note that a suitably detailed description of the analytical procedures is expected to be included in Module 3 of the Common Technical Document (CTD) whichever approach is used to identify ECs for analytical procedures.

The authors interpret the enhanced approach described in this paper to be fully aligned with the latter approach to identifying ECs, and therefore, ECs for an analytical procedure could be considered as analogous to an ATP (28). Furthermore, in many cases, it could be argued that procedures successfully validated according to the current ICH Q2 guidance could also have ECs described by their method-specific performance criteria.

Chapter 3 also describes how changes to ECs for manufacturing processes may have different reporting categories proposed by the applicant (prior approval or notification) depending on the risk associated with the process change. A similar risk-based approach could be adapted for reporting categories associated with changes to ECs for analytical procedures. When changes to procedures remain within approved ECs these should be managed solely within an applicant’s pharmaceutical quality system.

Following the initiation of Q12, FDA published a draft guidance that describes how the concept of ECs can be used to clarify the elements of a licence application that constitute a regulatory commitment (29).

In Chapter 4, PACMPs or comparability protocols are discussed. These are regulatory tools that exist in the European Union and United States, and the Pharmaceuticals and Medical Devices Agency (PMDA) has recently initiated a pilot program on PACMPs in Japan. While it is not required by Q12, the enhanced knowledge and understanding gained from applying an enhanced approach to analytical procedure development may be valuable in supporting proposals for “broader” PACMPs (e.g., those concerned with one or more changes to analytical methods to be implemented across multiple products and/or multiple sites).

The structured approach to analytical procedure changes described in Chapter 8 is not related to ECs for analytical procedures. It is intended to enable companies to follow this structured approach for changes to currently approved analytical procedures, whether they were developed using an enhanced approach or not, and without needing a prior regulatory submission before implementing the change to the analytical procedure. The approach incorporates good change management practices and ensures the revised analytical procedure is equivalent or better to the original. The scope of procedures where this approach may be used has some limitations, and a regulatory notification is required at the end of the change.
The past few years have seen the emergence of regional guidance on analytical procedures, for example, from FDA (30), European Medicines Agency (31), Brazilian Health Regulatory Agency (32), and Ministry of Health, Labor, and Welfare (33), which adopt some of the newer risk based/lifecycle development concepts. In June 2018, the ICH Assembly agreed to initiate development of harmonized guidance(s) for analytical procedure development and revision of Q2(R1) analytical validation Q2(R2)/Q14 (34). The first task for the working group will be to develop a concept paper and work plan and the authors of this paper look forward to the development of this ICH topic and its relationship to the ICH Q8–Q12 guidelines.

The current ICH Q2 guidance on the validation of analytical procedures was first published in 1994 and the text and methodology combined into the current ICH Q2(R1) guideline in 2005. Although the concepts in Q2 have stood the test of time, the initiation of the Q14 topic provides the opportunity to include elements of lifecycle management of analytical procedures and extend the concepts to contemporary measurement technique applications, for example with process analytical technology (PAT) or methods using multivariate models.

Conclusion
The publication of papers, stimuli articles, and case studies continue the active debate on the enhanced approach for development and application of analytical procedures. Recent concepts such as the analytical target profile and method operable design region are increasingly becoming established, with the ATP being a valuable tool to focus development of fit-for-purpose analytical controls and procedures (35).

Recent developments in the progression and initiation of ICH quality guidelines (ICH Q12, Q2 revision, and ICH Q14) show that the regulatory aspects of the development and lifecycle management of analytical procedures is likely to be of continuing interest in the coming years. Concepts associated with the enhanced approach, including the ATP concept and method control strategies, may provide useful input for consideration by the expert groups developing these harmonized global guidelines, and ultimately contribute to the development and supply of high quality medicines for patients throughout the product lifecycle.

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Technology transfer is a difficult process, whether it occurs between R&D and manufacturing within a single company, between an academic lab and a corporation, or between a manufacturer and a contract development and manufacturing organization (CDMO). Pharma’s folklore is full of stories about tech transfer failures: analytical techniques or processes that worked perfectly in the lab, yet failed on the plant floor, costing partners significant time and money, and derailing promising development programs.

Where a few decades ago, research department staffers might speak glibly of throwing a process “over the wall” from R&D to scaleup and manufacturing, today most organizations realize how wasteful that approach has been and are approaching tech transfer in a much more systematic and collaborative way. Crossfunctional teams are usually the rule, with representatives from each major operational group (e.g., quality, business, research, and operations) at the sponsor group taking an active role in moving projects forward.

In addition, best practices often call for minimizing the number of tech transfers required involved in the development of a drug, says James Bernstein, principal of Live Oak Pharmaceutical Services. This approach depends on careful contract partner selection, he says, to ensure that the CDMO’s strengths are fully leveraged at each stage. Typically, he says, a sponsoring drug company will opt to work with a smaller contract partner for the initial development and formulation, then design the process so that only one tech transfer is required, he says, so the project can move straight from development to Phase III. “If we plan the process well, we can get away with only one tech transfer, but you’ll always have at least one,” he says.

Tech transfer is also the best time to consider scale-up type issues, and to take stock of risks based on the technologies and equipment that are available, says James Blackwell, principal of the Windshire Consulting Group. “By understanding the sensitivities and behaviors of your system, you can start to predict behavior,” he says.

Currently, a growing number of companies are starting to use novel technology to help improve and speed tech transfer. Merck, for example, tested the use of augmented reality to move an analytical process between sites, and found that it improved efficiency by 10% (1). By allowing partners in the transfer to interact directly, to troubleshoot and share “tribal knowledge” (i.e., expertise gained by people experienced in operating the equipment or working with the technology that cannot be written into a training manual or other typical documentation), the technology can help improve communication and eliminate travel time and expenses (2).

Joseph Szczesiul, director of technical services for UPM Pharmaceuticals, recently shared best practices for tech transfer with Pharmaceutical Technology.

Keep a development narrative
PharmTech: What are the crucial elements to doing tech transfer correctly,
and when should their foundations be established?

**Szczesiul:** The best foundation for tech transfer success is complete formulation and process development. You cannot correct formulation deficiencies during tech transfer, and process optimization can only provide limited improvement. An inadequate enteric coating, for example, or a wet granulation with insufficient binder, can only be improved incrementally by process changes. The big fix comes from formulation change, which needs to be done early in the development process.

To step back even further, a development project needs clear and complete goals, which then lead to a strategy, and then to a plan of work. The obvious goals are to succeed in the clinic, to file your application, get approval, and start selling product. But a product also needs to pass validation. It must also be physically and chemically stable, and will need to succeed in routine manufacturing and to meet regulatory requirements.

A good practice is to maintain a development narrative over the life of the project. This becomes a reference, but it is also a tool for periodic review. It should include the goals for each stage of development. It should list the batches made, their purpose, and their outcome, and also list all issues and problems encountered with each one.

All issues should be resolved before proceeding to the next development phase. At the end of each phase, call a team meeting, review the development against the goals for that phase, and determine whether the project is ready to move further down the path. In that way, you keep returning to your overall strategy, and your idea of big-picture success.

**A little knowledge (transfer) is a dangerous thing**

**PharmTech:** What are the biggest mistakes that pharmaceutical companies and inventors most often make when approaching tech transfer? What do they often appear to overlook or leave out?

**Szczesiul:** Incomplete knowledge transfer to the CDMO is a consistent problem with tech transfer projects, and projects are often delayed due to incomplete information being provided. Effective technology transfer requires access to relevant information about the process that is being transferred.

Client companies must provide as much information as possible to their CDMO, since the client possesses all of the documented and undocumented product and process knowledge at that phase of the project. Ideally, knowledge transfer takes place through the provision of a technology transfer document package, as well as through routine ongoing communication.

**“... The CDMO’s technical leads should be able to explain not just what they are doing, but why ...”**

—**Joseph Szczesiul**

In addition to the ‘hard’ data transfer, it is important for client companies to transfer their peripheral and soft, experiential knowledge. The client’s experts that know manufacturing, analytical, and safety aspects of the product should be on the project team so they can provide continued review and input.

**PharmTech:** What should client companies ideally focus on, and how should they be staffing and managing these projects?

**Szczesiul:** Client companies should focus on information transfer, on having a clear regulatory strategy, and on developing an appropriate plan of work in conjunction with their CDMO. A tech transfer plan of work establishes the steps to be implemented to generate all of the information and data necessary for successful regulatory filing. It must meet regulatory agency expectations for the application and answer questions specific to the product being transferred.

**PharmTech:** Can you share any tech transfer war stories?

**Szczesiul:** Years ago, I worked on a project where nearly, but not quite all, of the required information was communicated by a sponsor. This project involved the site transfer of an approved Wurster-coated product. It was sustained-release, with the polymer dissolved in a flammable solvent.

Our fluid bed was from the same equipment manufacturer, it was explosion-proof, and it matched the bowl size of the fluid bed at the originating site, so it was assumed when the development contract was signed that no process development work would be needed, just a confirmation batch to verify a successful run using the parameters in the original batch record.

However, two significant issues arose after we finally received a copy of the batch record. First, the originating site used the same size bowl as our fluid bed, but it was connected to a different expansion chamber to a model that was two sizes larger than ours. This meant that our filter chamber was several feet shorter than theirs, so we had to reduce airflow, to avoid driving product up into the filter.

Second, we learned that the other site had a sealed air system with solvent recovery, and purged their system with nitrogen to prevent combustion of the solvent. We did not have either capability, and for safety and insurance reasons, our maximum spray rate could not exceed 40% of the original spray rate. A new coating process had to be developed. So the project exceeded its original scope, required unexpected process development work, and caused an unexpected delay for the client.

**PharmTech:** For virtual companies, and even nonvirtual companies that outsource most key functions, what is essential to coordinating efforts and ensuring success?

Contin. on page 48
It is no secret that staff training remains a weak spot in many corporate strategies. In 2017, 30% of the 40 warning letters that FDA issued for data integrity deficiencies directly referred to inadequate training or training requirements (1).

A number of challenges prevent life-sciences companies from developing more effective training programs. One major problem is the way training-related data have been traditionally organized. For example, most pharmaceutical and biopharmaceutical companies use one system to manage standard operating procedures (SOPs) and other knowledge-management documents, and a different system to manage training. Ideally, the two areas should be connected, or a barrier will be created between activities that should be closely aligned.

For example, consider the specialty pharmaceutical company Tolmar, which had built a custom application to manage and track compliance-based training requirements, but used a cloud-based system to administer various other types of training. The company’s in-house learning management system (LMS) required extensive configuration and integration, as well as ongoing validation support.

“We have around 1600 documents that 700 employees across the organization need to be trained on. Managing this workload across two applications—our cloud-based document management system and in-house LMS—is complex and requires a lot of overhead,” says Joe Miller, Tolmar’s vice-president of information technology.

Simplified role-based training can lead to better quality metrics and compliance.

A similar lack of alignment is often seen between training systems and corporate business objectives, which can make it difficult to link training outcomes with concrete goals such as reducing manufacturing-related deviations or other quality events. Rather than viewing training as a corporate expense, managers should be able to see how effective training programs directly influence critical quality metrics. As a result, more life-sciences organizations are rethinking training, and starting to view it as a strategic part of quality assurance and control, and overall business goals.

A growing number of pharmaceutical companies are now working to modernize training programs, to align training with compliance documentation and corporate strategy. This requires unifying processes across quality, content, and training systems for improved quality management. In a unified, end-to-end approach to training, users first identify and revise the documents that would be most significantly impacted by a deviation. Then, when a quality event does occur, the system automatically triggers and assigns training tasks to the right people. In this scenario, training is connected to document versions, change-control processes, and quality events, helping to support broad organizational goals to improve quality metrics.

Getting to an end-to-end approach will take some time and effort, but following the five steps below will lay the groundwork for making training a strategic asset.

**Develop a bill of learning that attaches trainable behaviors to key quality metrics**

Bridging the gap between a business goal and training starts with a bill of learning, which breaks the goal down into discrete, measurable learning objectives for a specific skill set. Educational initiatives can then be tied to a company’s strategic direction, helping improve critical metrics. In addition, a bill of learning can help demonstrate the impact that training has on the overall business.

In this bill of learning (Figure 1), a pharmaceutical company has encoun-
The company decides that to reinforce individuals’ ability to follow SOPs without deviation, the bill of learning makes it easy to understand the impact of not following proper SOPs, which helps reinforce the importance of following approved procedures without deviation.

“With a bill of learning, companies can break a strategic objective into specific learning components and link the learning outcomes back to the organization,” says Karl Kapp, director of the Institute for Interactive Technologies and professor of instructional technology at Bloomsburg University. “In doing this, companies effectively connect quality and compliance, gathering metrics that can be measured against corporate objectives to continuously improve quality processes.”

A modern solution unifies training and quality management, enabling teams to track quality metrics and link them back to training to ensure effectiveness. Nationally or globally dispersed organizations can bring together SOPs, quality processes, and training with complete transparency. In this example, companies identified documentation related to this specific deviation and built training around the recurring behavioral gaps. With a bill of learning, training is also attached to a corporate objective to ensure alignment across internal and external stakeholders.

“At Tolmar, one of our quality goals is ‘do it right the first time,’” and a cloud-based training solution provides a strong foundation for this goal,” says Miller. “Many pharmaceutical companies have a program or process for SOP training, but most of these programs are inefficient. A training system in the cloud that’s connected to quality processes and content helps streamline our training, so we are more confident that critical documents have been read and understood.”

**Define roles for role-based training**

Once a bill of learning has been established, the next step is to specify learner roles—the foundation for role-based training. Modern role-based training uses a combination of job responsibility, function, and hierarchical level within the department or organization.

With legacy technologies, learner roles are often exclusively tied to a specific job title or ID, limiting the ability to deliver precise content to each person. People are often undertrained or placed in more than one group and over-trained. Both situations present compliance risks. Without the ability to deliver appropriate, contextual content, it is almost impossible to build a flexible and scalable training program while ensuring compliance.

For example, without role-based training, every employee in a quality manufacturing department receives the same curriculum, such as training on 85 SOPs and work instructions. With flexible, role-based training, organizations deliver tailored content to specific roles such as a quality manager, quality assurance associate, or documentation specialist. Instead of being trained on all 85 SOPs and work instructions, a quality assurance associate would only train on the 25 that are specific to his or her role. Assigning a specific curriculum to each role helps to reinforce the learning objectives that directly connect to those responsibilities.

Defining learner roles is a critical first step in implementing a role-based training curriculum, and it starts by asking questions like, “Is each role specific to one department, job, or function, or combination of these attributes?” or “Which roles are applicable to the behaviors identified in a bill of learning?” The answers will help teams tailor training programs to ensure that the right content reaches the right people, to do the right job, at the right time.

Modern training solutions connect training to learner roles in an end-to-end process within the quality system. A quality document is tagged as required training and, in the event of a deviation,
After determining learner roles, organizations can apply microlearning techniques to break down larger and more complex SOPs to develop hyper-focused content for their role-based training programs. For example, if many deviations have been linked with a failure-to-follow a key SOP, companies can then divide that SOP into smaller, targeted learning assets to help staff focus on the necessary skills. An organization could create a short, two-minute video to demonstrate only a specific cleaning procedure to support a longer SOP. Since each task is connected to a larger instructional objective, microlearning reinforces the right behaviors for better performance that improve strategic quality objectives.

“Performance support and learning are inextricably linked,” says Kapp. “In any organization, we learn because we want a certain outcome. We want learners to perform an action correctly, so microlearning can really be an invaluable tool for supporting improved performance.”

Microlearning in a unified quality system helps make the learning journey holistic, instead of introducing learning as a series of one-off events. Once a quality procedure has been revised, the system automatically re-assigns training for that SOP based on the pre-determined learner roles. This approach helps ensure that learners are not only reading and understanding documents, but also applying that knowledge to their daily tasks effectively.

“We want to expand our program to go beyond simply training on SOPs and see if specific training has a real impact on an individual’s performance,” says Miller. “With our cloud-based application, we can use concrete evidence, such as results from on-the-job training, to assess an employee's comprehension. Doing it right the first time will help us avoid rework and costly errors.”

**Deploy training in the flow of work**

Microlearning can only be as effective as when, where, and how it is deployed. Companies can expect better results from training programs by shifting from individual, content-driven events to learning that is deeply contextual, social, and embedded into real work (2).

Considering how much information is consumed via technology every day, meeting learners where they learn best—in the flow of their work and day-to-day life—is crucial. The average person checks his or her smartphone nine times an hour and pays attention to specific content for less than seven seconds (2). In fact, smartphones dominate as learning technology, and recent research has shown that 70% use their mobile devices to learn (3).

Where and when learning takes place should also be considered when deploying training materials. A large percentage of learning happens during the workday, with 27% of learners consuming content during the work commute and 42% at work. Since more than half of individuals learn at the point of need, microlearning can greatly impact learning objectives by delivering learning events more rapidly and frequently.

“When a learner needs to retrain on the appropriate steps to execute an action, they can access training in the flow of their work when they need it most, without delay or interruption,” says Kapp. “This is an example of how microlearning and the strategic goals of an organization can come together to create the right learning environment.”

One solution for training enables both learners and trainers to focus on the right content, at the right time, across devices. More pharmaceutical companies are using tablets in manufacturing facilities so people can access the relevant work instructions they need at any station on the shop floor. Employees ensure they are performing the right action while they work and can reference training content at any time, on any station. For example, a video that demonstrates cleaning procedures can be available via a smartphone so learners can train on how to clean machinery as needed. By connecting learners with training content at the time of need and according to their learning habits, companies can better change behaviors to decrease quality events.

**Generate insight and take action to realize measurable impact**

Many organizations have encountered difficulties generating comprehensive reports around training or qualification tasks and how they are related to compliance. Training tasks live in a different place than the training content, such as in a document management system, email, or in multiple learning platforms, reducing visibility.

End-to-end insight in a unified system enables companies to understand how training is related to quality objectives to make better, more informed decisions. Once a training initiative has been completed, teams generate reports that include which critical content and version are associated with deviations, when corresponding training materials linked to a deviation were consumed, and whether the number of deviations decreased as a result.

With quality processes, documentation, and training unified in one solution, quality teams can then effectively report on strategic metrics and the return on investment of the training program. A bill
of learning in a unified system provides a direct correlation from the discovery of an issue to the deployment of training and a tangible process improvement.

“Direct integration between our training, documents, and processes allows us to measure the impact of training and determine if training is helping us meet strategic goals,” says Miller. “We can schedule training for new and revised documents, link quality events like corrective and preventive actions to training tasks, and measure the results. These new capabilities, only possible with a unified platform, will eliminate manual processes and allow us to stay dynamic and better align our processes with quality objectives.”

Strategic training to improve quality metrics
Corporate learning in life sciences has the potential, not only to improve productivity and reduce errors, but to also become an important source of strategic, competitive advantage (3). These five steps offer a starting place to drive continuous process improvement in quality. By continually breaking down a strategic objective into specific learning components, companies teach to those components and apply the outcomes to the organization. At the conclusion of the process, teams provide metrics that are directly associated with the strategic advantage, measuring improvement and building better quality programs around a specific learning objective.

The cloud is enabling the industry to bring training and quality processes together and transform quality management. The results of doing so include saving time by accelerating internal audit preparation and onboarding team members faster, as well as improving compliance as more quality professionals can execute their jobs better. Correlating training results to quality objectives will enable organizations to make more informed decisions and rethink training as a critical business strategy.

By connecting quality management and training in a single application and applying modern learning techniques, life-sciences companies can create an effective training program that’s measurable across the organization.

References
Impact of Non-Compliance on the American Healthcare Consumer

Sharon Ayd

GMP non-compliance can spill over and impact patient access to life-saving medications.

A previously published article (1) reviewed, in depth, the many options FDA has available to escalate the enforcement process when a biopharmaceutical company repeatedly violates the main regulatory standards for ensuring pharmaceutical quality (i.e., 21 Code of Federal Regulations [CFR] Parts 210 and 211, collectively referred to as the current good manufacturing practices [CGMPs]). When a biopharmaceutical company repeatedly violates CGMP requirements, FDA can force it to make specific changes. Under this severe form of escalation by FDA, it’s no longer a discussion about responses to FDA 483 notices or warning letter observations, it’s about a forced make-over. This process, known as Consent Decree (CD), exposes all the broken systems within a company. The impacts of FDA warning letters and CDs extend far beyond the biopharmaceutical company. Today, many times, the impact of a warning letter or CD is discussed only with regard to the effort exerted internally by the biopharmaceutical company to remediate FDA’s enforcement action against itself. This article discusses, in broader context, how non-compliance spills over and impacts the US healthcare system and the consumer.

Current snapshot of the American healthcare consumer

The US healthcare consumer is older than ever before. From 2012 on, the number of people in the United States turning 65 increased from an annual rate of approximately 2.6 million per year to approximately 3.5 million per year in 2015, a number that is forecasted to rise to nearly 4 million per year over the next decade (2). By 2020, retiring baby boomers will drive Medicare and Medicaid costs to 24% of the United States healthcare budget. As healthcare costs increase faster than economic growth, Medicare taxes and the Trust Fund will cover less and less. In 2016, US healthcare costs were $3.3 trillion. That makes healthcare one of the country’s largest industries, equaling 17.9% of gross domestic product (GDP). In comparison, in 1960, healthcare cost $27.2 billion, or just 5% of GDP (3).

The healthcare consumer is not just the patient, they are caregivers too. More and more people in the US are putting jobs on hold or otherwise impacting their lives to provide medical-related support to someone close to them. On Jan. 22, 2018, the Recognize, Assist, Include, Support, and Engage (RAISE) Family Caregivers Act (4) was signed into law. Providing care for a family member, partner, or friend with a chronic, disabling, or serious health condition, known as “family caregiving,” affects most people at some point in their lives. The need to support family caregivers will grow as the population ages, more people of all ages live with disabilities, and the complexity of care tasks increases. In 2013, about 40 million family caregivers in the US provided an estimated 37 billion hours of care to an adult with limitations in daily activities. The estimated economic value of their unpaid contributions was approximately $470 billion in 2013, up from an estimated $450 billion in 2009 (5).

Healthcare challenges in the US are not geographically blind. The healthcare delivery system in rural America is largely fragmented. The challenges affecting people living in rural areas are different than those affecting people in urban areas (6). These challenges are significant because approximately 51 million, or about 1 in 6, people live in rural areas of the US. The rural popula-
tion is also older; the rate of growth for seniors living in rural areas has tripled since the 1990s, and if the 80 million baby boomers living in the US continue to follow these migration patterns, the rural population of those age 55 to 75 is set to increase 30% between 2010 and 2020 (6, 7).

Rural Americans have the same issues as other healthcare consumers, only they are more extreme. They tend to have lower incomes, poorer health status, and are less likely to have health coverage through work because there are fewer large employers in rural areas. Consequently, rural consumers are also more likely to be uninsured and more likely to be covered by public rather than private insurance (7). When compared to urban areas, rural areas have higher rates of unemployment and poverty. Recent numbers show rural unemployment averaged 5.4%, while urban unemployment was 4.8% (7).

So, let’s examine some of the ways in which a pharmaceutical company’s failure to manage quality manifests itself outside the company and impacts the American healthcare consumer.

**How non-compliance impacts on the American healthcare consumer**

For purposes of this article, non-compliance will equate to FDA enforcement activity (i.e., warning letter or CD) against a biopharmaceutical company in the US. Operating under a warning letter or CD is a dire situation for the company and one where there is no certain predictability of the outcome. To really understand the magnitude of the warning letter’s or CD’s impact, one needs to take into consideration the many and various modes in which the negative consequences can be realized externally and how this impacts the American healthcare consumer.

**Figure 1** illustrates the ways in which non-compliance effects can propagate internally and externally to the company. This article focuses on those external effects as they impact the American healthcare consumer. To better understand, think of **Figure 1** as a “Tile Slide.” The first three tiles of the first row represent different categories of negative impact to the biopharmaceutical company, while the last tile represents negative impact to the healthcare consumer. Each subsequent tile or row in a column describes a more specific negative effect.  

**Sterile injectable drugs**

Biopharmaceutical companies manufacture many different drug formulations. Drugs that will be given to a patient by intravenous injection must be manufactured under conditions suita-
Quality: Risk Assessment

ble for human use. They must be manufactured to standards of quality, purity, and sterility that are uncompromising or the patient could be harmed. Interpretation of the GMP guidelines for ensuring integrity of injectable drugs can be a challenge, leading to questioning of how to achieve the standards. The manufacture of sterile injectable pharmaceuticals suitable for human use is complex. Biopharmaceutical manufacturers must ensure the necessary quality parameters described within the United States Pharmacopeia are met. Substandard injectable drugs can arise through inadequate production processes including unintentional use of inferior APIs or excipients, manufacturing processes that cause contamination or do not adequately ensure sterility, and inadequate packaging design or quality. If such medicine left the manufacturing facility it would most certainly be recalled.

How non-compliance officially gets recognized
The main regulatory standard for ensuring pharmaceutical quality is collectively referred to as the CGMP regulations for human pharmaceuticals. It’s not only the CGMP regulations matter; how companies interpret and embrace them is of equal, if not more, importance. CGMPs place emphasis on product quality and compliance with the regulations.

FDA’s Office of Regulatory Affairs is the lead office for all field activities, including inspections and enforcement. FDA conducts several types of inspections to help protect consumers from unsafe products: pre-approval inspection, routine inspections of a registered facility, and “for-cause” inspections.

After FDA completes an inspection, company management may receive an FDA Form 483 (8) when an investigator(s) has observed any conditions that, in their judgment, may constitute violations of the Food, Drug, and Cosmetic (FD&C) Act, related Acts, and applicable sections of 21 CFR 210 and 211. Observations are made when in the investigator’s judgment, conditions, or practices observed would indicate that any food, drug, device, or cosmetic has been adulterated or is being prepared, packed, or held under conditions whereby it may become adulterated or rendered injurious to health. FDA Form 483 notifies the company’s management of objectionable conditions. Companies respond to the 483 in writing with their corrective action plan and implement schedule. The 483 is closed when the company receives their establishment inspection report. Unfortunately, there are companies that either do not follow through on their commitments or they do so too slowly. If circumstances merit, FDA can choose to escalate the situation by serving the company with a warning letter.

Typically, FDA’s practice is to give individuals and companies an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action. The warning letter is FDA’s principal means of notifying regulated industry of violations and achieving prompt voluntary correction. Following are some of the factors FDA uses to determine whether to issue a warning letter (9):

- The company’s compliance history (e.g., a history of serious violations, or repeated failure to prevent the recurrence of violations)
- The nature of the violation (e.g., a violation that the firm was aware of [was evident or discovered] but failed to correct)
- The risks associated with the medical products (i.e., drugs and the potential that such risks could cause harm to patients).

Non-compliance and supply interruptions
Many drug shortages are of sterile injectable drugs and can be traced to supply disruptions caused by company manufacturing facilities slowing or halting production to address quality issues. The number of new shortages has generally decreased since 2011, while the number of ongoing shortages remains high. In 2015, the number of ongoing shortages that began in prior years was up compared to 2014 at 291 and 277, respectively. The number of new shortages being first reported in 2016 was down compared to those reported in 2014 at 136 and 179, respectively (10). Shortages of sterile injectables can be associated with other factors: a decline in the number of manufacturers; failure to comply with CGMP standards, resulting in a warning letter which causes supply disruptions in the first place; and/or prolonged time under warning letter remediation when the manufacturer either cannot manufacturer drugs or the situation warrants that each drug lot must be released only after extensive oversight and review. Another reason is that many of these are generic drugs that can have a relatively low profit margin and manufacturers are less likely to increase production. Regardless the reason, all of these situations only exacerbate already existing supply disruptions.

Characteristics of the sterile injectables industry may make these drugs susceptible to shortage when the number of suppliers decreases. A manufacturer, for example, may decide to permanently discontinue an unprofitable product, or the unavailability of raw materials may lead to production delays. Further, failure to comply with CGMP standards resulting in a warning letter could also trigger a supply disruption if a manufacturer chooses to temporarily shut down production to correct the conditions that led to a warning letter. In this industry, there is limited inventory in the supply chain, manufacturing capacity is constrained because production is scheduled months in advance. New manufacturers must receive regulatory approval before entering the market, and the production process is complex. After a supply disruption for any reason, if other manufacturers are not able to increase supply in a timely manner, a shortage may ensue.

There are specific characteristics of the sterile injectables industry that make these drugs susceptible to shortages (11).

Limited inventory. The use of just-in-time supply demand can increase the vulnerability of the supply chain to
shortages. It is not uncommon for manufacturers to have approximately two to three months of inventory available. Wholesale distributors may have one month, and providers may only have a few weeks of inventory. Hence, when a manufacturer stops production, a shortage can result quickly.

Regulatory approval. A new manufacturer could decide to supply the market but usually can’t enter quick enough to produce more drug and remedy the shortage. This is because FDA’s approval of an abbreviated new drug application (ANDA), which is a requirement, can take more than a year. Even if existing manufacturers of the drug could ramp up their own production, they would need FDA approval if changes to manufacturing conditions or processes were made that have a potential to adversely affect the identity, strength, quality, purity, or potency of the drug, before the additional drug manufactured under the new conditions can be marketed.

Manufacturing complexity. Expensive and specialized equipment is required to manufacture drugs, and production processes are complex, particularly for sterile injectables (12). Maintaining sterility throughout the production process is particularly important for sterile injectables because serious harm can occur if non-sterile drugs are injected into patients. Some generic sterile injectables need to be manufactured on lines or in facilities dedicated solely to those drugs, thus creating challenges for new manufacturers to enter the market.

Constrained manufacturing capacity. The generic sterile injectable drug industry is filled with several players. It’s not uncommon for a manufacturer to produce numerous and different drugs on only a few manufacturing lines. As a result, this leaves little flexibility when one manufacturer ceases production of a particular drug. Adding yet more constraint is that many times the production schedule of each drug is planned for up to a year at a time. This leaves little opportunity for sudden changes in production schedule to produce additional quantities of a drug in shortage.

Characteristics of the sterile injectables industry may make these drugs susceptible to shortage when the number of suppliers decreases.

When a supply interruption becomes a drug shortage

Drug shortages in the US are a serious public health concern and have been for many years. Shortages caught the attention of the US Congress and resulted in a provision in statute for the US Government Accountability Office (GAO) to review several aspects of drug shortages. The period covered was 2010 to 2015, and GAO’s review was published in an extensive report to Congressional committees in July 2016 (10, 13).

Shortages of sterile injectable anti-infective and cardiovascular drugs during 2012, 2013, and 2014 were strongly associated with the following factors: a decrease in the number of manufacturers, sales of a generic version, and the failure of a manufacturer making the drug to comply with CGMPs resulting in a warning letter. For each factor, the GAO report estimated a percentage point increase in the probability of a shortage. Their estimates showed that the presence of a single factor increases the probability of a drug shortage by as much as 16.8 percentage points from what the model otherwise predicted (10). The strong association between shortages and both a decrease in the number of manufacturers and the failure of a manufacturer to comply with CGMPs resulting in a warning letter suggests that shortages may be triggered by supply disruptions.

For the drugs reviewed in the GAO report, the association between non-compliance resulting in a warning letter and shortages is largely driven by the structure of the generic injectable manufacturing industry. In this industry, manufacturers produce multiple drugs, and so one manufacturer’s failure to comply with that results in a warning letter could affect many drugs. For example, 69% of the 118 drugs in the GAO study were manufactured by at least one of nine companies. Thus, if one of these nine companies failed to comply with CGMP standards, many drugs could be affected (14, 15). In 2012, one manufacturer that received a warning letter manufactured 22 drugs just by itself. While the strong association between non-compliance resulting in a warning letter and shortages could support the thought that FDA enforcement triggered some shortages, it could also support the thought that there were growing CGMP problems and possibly related quality concerns that both precipitated the warning letters and led to shortages.

Additionally, the finding that sales of a generic version were associated with shortages suggests that relatively low profit margins may also trigger shortages for sterile injectables. Specifically, compared with drugs for which there were only brand-name sales and thus only one supplier, drugs sold generically may have multiple suppliers and relatively lower profit margins. The 88 drugs in the GAO report sold generically were available from an average of four suppliers during 2013, and 10 drugs had eight or more suppliers. Other researchers have found that prices, and consequently profit margins, decline for generic drugs as the number of suppliers increase (16). Relatively low profit margins may cause manufacturers to exit the market for less profitable drugs in favor of more profitable ones or may make it unprofitable to increase supply, which could make the market vulnerable to shortages.
Quality: Risk Assessment

Emergency response drug shortages
In US emergency rooms, some of the most common injectable painkillers (e.g., morphine, hydromorphone, and fentanyl) are in short supply. These are first-line choices and vital. What’s challenging is that second-line drugs are out, too. In 2017, half of the medications in drug shortages were for critical care (17). While the majority of the drugs involved in nearly 2000 drug shortages from 2001 to 2016 had an alternative available, one-quarter of the time those alternatives were also on the FDA shortage list. The most common drugs in those shortages were for infectious diseases.

The average length of shortages for drugs used in ambulatory medicine is more than seven months (18). First responders, including some fire departments, have come up with different solutions, including diluting the concentration of a medication on the scene of an emergency and using varying packaging and delivery methods for those drugs (19). They resort to using less potent medication, such as morphine during a fentanyl shortage. Or, it could involve not giving the most basic, benign medication: a saline drip to rehydrate patients or dilute drugs given intravenously. Other ways to address a shortage is to encourage field personnel to provide treatment only when needed as opposed to prophylactic measures (i.e., start the IV if the patient needs the IV, as opposed to starting an IV just in case something should happen) (19).

As for saline, while the smaller 100mL to 500mL bags are in short supply, the larger one-liter bags are used. Or, if they’re being used to deliver medication, it can be given via syringe, although this takes up more of a caregiver’s time. Overall, it’s part of a balance that healthcare providers face in delivering needed medication to patients while still preparing for the unknown: local disasters, epidemics, or even a worsened drug shortage.

Impact of drug substitution
When available supplies of prescription drugs are insufficient, patient care may be adversely affected. Drugs in shortage include those that are essential therapies, such as antibiotics, chemotherapy agents, cardiovascular drugs, and pain medications. Shortages can result in delayed patient care and medication errors. They may also result in rationing, which can lead to the use of less effective treatments and force healthcare providers to make difficult choices, such as deciding which cancer patients should start or complete a round of chemotherapy (20). Drug shortages can impair patient care, raise healthcare costs, and hamper clinical trials. Hospitals receive a daily report that shows which drugs are in short supply. In any week, injectable opiates, IV solutions, and a variety of other drugs widely used treatments for heart surgery, dehydration, pain management, nausea, and other ailments compromise nearly all types of care, appear on the drug shortage list.

Emergency physicians must spend more time working around drug shortages. That means they spend less time with the patient, who may receive a more expensive but less effective treatment.

More than one-third of emergency physicians said patient outcomes have been negatively affected as a result. Nearly 90% said they have had to take time away from patients to deal with these shortages while 97% said they had to substitute medications. Drug shortages are expensive (20), and they often lead to mistakes. Providers have had to reconfigure crash carts and other trauma toolkits, which means that it may take longer for first responders to find a drug during an emergency. All this requires thorough staff training, new processes, and constant surveillance.

Conclusion
Drug shortages in America exist for a varying number and combination of reasons that are complex and interrelated. While some of many reasons why drug shortages exist may not be directly linked to non-compliance, it seems that non-compliance is one of the most common reasons that puts things into motion. Ultimately, it is incumbent on the companies and FDA to find new ways to work together to manage these situations before they arise.

References
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Antibody-based drugs offer new mechanisms of action and greater specificity.

The rise of antibiotic-resistant bacteria is recognized as a significant threat to the future practice of medicine. Continually rising resistance rates have resulted in infections with bacteria resistant to all existing antibiotic treatment options. There is concern that if the current treatment system remains unchanged, the resistance epidemic could push the world into a post-antibiotic era.

Alternatives are therefore needed to replace current small-molecule antibiotics. Given that the development of resistance is a natural form of evolution for bacteria, the challenge is to find new drugs that kill bacteria in a way that dramatically slows down their ability to counteract them. Biologic drug substances—monoclonal antibodies (mAbs) in particular—may be a key component of the solution.

Resistance is multifaceted

Regardless of the antibiotic, resistance will develop, according to MedImmune’s director of microbial sciences Bret Sellman. “Most available antibiotics are related to natural products for which resistance already exists in nature,” he explains. Bacteria also divide rapidly, which increases the likelihood for antibiotic-resistant mutants to evolve.

In addition, over the past four decades there have been few truly novel antibiotics, according to James Levin, director of preclinical development at Cidara Therapeutics. “We have been targeting the same limited subset of essential proteins, and therefore, bacteria have ample opportunity to evolve and become resistant to entire antibiotic classes over time,” he observes.

Sellman argues that development of antibiotic resistance has less to do with the structure or chemistry of antibiotics than it does their method of attacking a pathogen and their widespread use in modern medicine and farming. “By killing bacteria directly, antibiotics select for the outgrowth of resistant mutants. In addition, the misuse of antibiotics to treat viral diseases (e.g., the common cold) unnecessarily exposes patients and their bacteria to antibiotics and fails to treat the actual disease being experienced. This ease of access only increases exposure and subsequently the risk of resistance,” he asserts.

Resistance can arise from chemical modification of the antibiotic by bacterial enzymes or mutations to the antibiotic target, adds Levin. He also notes that bacteria are able to swap genes that impart antibiotic resistance with other bacteria, allowing resistance to spread rapidly.

Adding to these escape mechanism issues, Levin points out that gram-negative bacteria are intrinsically resistant to many antibiotics because they possess an outer membrane that is impermeable to most drugs—and they can mutate to reduce permeability further when under selective pressure.

The problem with broad-spectrum antibiotics

There is an additional problem associated with the use of broad-spectrum antibiotics: they kill not only harmful pathogens, but “good” bacteria that make up the microbiome within humans. Doing so results in the development of resistance in the target pathogen as well as the members of healthy microbiome, which can then transfer resistance to pathogens they encounter, further spreading the problem, according to Sellman.

Damage to the healthy microbiome can have significant consequences as well. “Killing of the healthy microbiome has been linked not only to the development of Clostridium difficile diarrhea but also diabetes, obesity, immune defects, and antibiotic resistance spread through gene transfer,” he says.

Pathogen-specific strategies

While antibiotics will always play an important role in saving and preserving life, the growing antibiotic resistance epidemic and increasing understanding of the adverse effects of broad-spectrum antibiotics on the healthy microbiome necessitate the development of alternatives such as pathogen-specific strategies to prevent or treat bacterial infections, according to Sellman. “We firmly believe that moving away from traditional small molecules is the path forward in antimicrobials research,” Levin agrees.
Most efforts are focused on new drugs based on mAbs because of their specificity. “Such targeted antibacterials should have reduced toxicity, cause less harm to patients’ beneficial microbiomes, and not promote resistance in bacteria not targeted,” Sellman comments.

Antibacterial mAbs also directly neutralize bacterial virulence mechanisms and engage the patient’s immune system, according to Sellman. “By boosting the immune system to kill the pathogen rather than killing the bacteria directly, the emergence of resistance might be reduced,” he explains.

Cidara Therapeutics is developing antimicrobial antibody-drug conjugates (ADCs). “These bispecific molecules capitalize on the potency of antibiotics coupled with the beneficial aspects of an effective and robust immune response and can be designed with a prolonged half-life,” says Levin. He believes that any antimicrobial, including small molecules, that binds to a surface or cell-wall component of the bacterium is a viable candidate for conjugation to an antibody fragment crystallizable (Fc) region.

In addition to antibody-based drug candidates, Sellman notes that researchers across industry and academia are also exploring phage lysins and viral phage approaches as alternatives to small-molecule antimicrobials.

**Antibacterial biologics require new thinking**

Development of mAb antimicrobial drugs does not come without challenges, but those difficulties are not solely in the scientific arena. “In order to realize the promise of biologics in infectious disease, we need to evolve the way we plan to manufacture and diagnose for these medicines,” Sellman states. Because antibacterial mAbs would likely be most effective in the earlier stages of infections, a move to integrate mAbs into the mainstream infectious disease protocol would require a commitment to more rapid diagnostic methods.

In addition, he notes that because pathogen-specific mAb treatments must account for bacterial strain diversity and the expression of multiple virulence determinants by the infecting pathogen, mAb combinations may be required for optimal efficacy.

The higher cost of biologic antibiotic drug substances compared to their small-molecule counterparts could also be an issue, according to Levin. His hope is, though, that the significantly longer half-life that should be achievable for biologic antibiotics, including ADCs, will enable less frequent dosing and thus offset the higher cost.

**An ADC approach**

Cidara Therapeutics set out to develop ADC antibiotics that exert a direct killing effect on the pathogen; engage the immune system, bringing a second mechanism of killing into play; potentiate standard-of-care antibiotics by attacking the bacterial cell wall and allowing them to penetrate the cell more effectively; and have superior (antibody-like) pharmacokinetic and distribution properties.

The company conjugates surface-acting antimicrobials (targeting moieties [TMs]) to Fc regions of human antibodies using non-cleavable linkers. The bispecific Cloudbreak ADCs exert direct killing activity on bacteria while targeting the cell for destruction by the immune system, according to Levin. “We believe that by developing drugs with a dual killing mechanism we will reduce the opportunity for the target pathogen to develop resistance. In addition, since our TMs do not have to reach the inside of the cell to kill the bacterium, we avoid the daunting problem of having to breach the bacterial membrane in gram-negative bacteria,” he says. In addition, because antibodies can remain at effective concentrations in plasma for a month or longer, Cidara believes its ADCs can ultimately be engineered to achieve a similar half-life.

The company recently demonstrated proof of concept with an ADC comprising a peptidic antimicrobial conjugated to a human Fc. “Although not our final drug candidate, this ADC was efficacious in murine *Acinetobacter* and *Pseudomonas* pneumonia models. It also demonstrated a much longer half-life than the polypeptide alone,” Levin notes. In-house characterization by Cidara’s immunology team further demonstrated the ability of this conjugate to successfully engage the immune system to enhance bacterial killing. Some of this work was performed in collaboration with Professor Ashraf Ibrahim at UCLA and has yielded important insights into the mechanism of action of ADCs.

The Cloudbreak ADCs are in preclinical development, but Levin expects a clinical candidate to be nominated in 2019. Current efforts are focused on evaluation of lead candidates in preclinical toxicology studies and exploration of Fc modifications to further extend *in-vivo* half-life. The company received a National Institutes of Health grant in 2018 in conjunction with Professor David Perlin at Rutgers that should accelerate the pace of its ADC program, according to Levin. Cidara is also applying its Cloudbreak technology to the development of antivirals.

**Two mAbs in development**

Within MedImmune, the global biologics research and development arm of AstraZeneca, two Phase II mAb assets are in clinical testing. MEDI4893 (suvrotxumab) is under investigation for the prevention of *Staphylococcus aureus* pneumonia in intensive care unit patients, while MEDI3902 is being developed for the prevention of *Pseudomonas aeruginosa* pneumonia in intensive care unit patients.

“As we continue to explore this field, we are constantly learning about the critical role of the commensal microbiome in maintaining overall health, and even the role it can play in possibly treating certain diseases. With this understanding comes a commitment to exploring new therapeutic options that avoid damaging these beneficial bacteria. The targeting specificity of biologics offers tremendous promise in making this goal a reality,” Sellman concludes.
Patient training devices used to ease anxiety related to the use of autoinjectors and prefilled syringes may offer industry data that can be used to develop and/or enhance these and other types of combination drug products. Pharmaceutical Technology spoke with Elizabeth Hawkins, Director of Marketing at Noble, about how Noble’s advanced, multisensory patient training devices may benefit industry and patients.

The benefits of patient trainers
PharmTech: What are autoinjector and prefilled syringe trainers designed to do?
Hawkins (Noble): Pharmaceutical manufacturers, physicians, patient advocates, payers, and other industry stakeholders have come to realize the importance of training devices as an effective way of familiarizing patients with the experience of injection and overcoming such problems as needle anxiety. To combat these issues, Noble has developed drug delivery device trainers that replicate the appearance and functionality of real autoinjectors and prefilled syringes, including the sensation of the needle entering the skin. Additionally, Noble has incorporated ‘smart’ features into some of its autoinjector trainers that can work in tandem with smart devices to provide instructions and feedback in real time to patients and their doctors. The purpose is to support patients who self-inject by offering them the opportunity to practice before self-injecting, or even practice between doses to combat natural memory decay. By practicing with these trainers, patients understand what using the real device will feel like and gain valuable insights that can guide them when they actually self-inject.

Noble has conducted various studies on the benefits of trainers for patients. Some of the most striking statistics tell us that almost two-thirds—or 64%—of patients report having a training device to practice with at home would help decrease their anxieties around self-injecting. Likewise, 90% stated that, on a scale of 1–10 (with 10 being the highest), a training device is at least a 7 in terms of importance when learning to self-inject.

PharmTech: How do such training devices benefit manufacturers?
Hawkins (Noble): Pharmaceutical manufacturers stand to benefit from the new generation of realistic trainers, as proper administration resulting from training may positively impact adherence and therapeutic effectiveness. As patients’ and prescribers’ positive perceptions of a combination product increase relative to the use of trainers, it can be argued that they will increase their usage of such a product and become brand-loyal.

With clinical studies and smart training devices connected to a digital ecosystem, it is feasible for manufacturers to study the ways in which patients are utilizing trainers, observe the most common usage errors, and then seek to incorporate modifications (such as improved ergonomics) into the design of future generations of self-injectable devices with the goal of helping patients avoid usage errors.

PharmTech: With AdhereIT, data can be collected on actual injections as well as trainers. What was the reason for introducing this capability? How might these data be used?
Hawkins (Noble): Knowledge is power, and with the digital transformation of the healthcare infrastructure, there is critical information to be gained through monitoring patient adher-
An important part of monitoring adherence is ensuring patients continue to utilize autoinjector devices properly throughout each step of treatment. This starts with training and onboarding and is important all the way through the drug therapy treatment to ensure successful injection each time. The advantage presented by AdhereIT is that, by being compatible with a wide range of commercially available devices, data on continued usage can be collected regardless of the autoinjector platform.

Most obviously, for patients, the use of AdhereIT may provide the informative feedback that encourages them to follow prescribed dosing regimens for longer periods of time. For their part, healthcare practitioners can provide new patients with a tool that offers an added layer of assurance that self-injecting is being performed properly. The data collected by AdhereIT can be shared with the practitioner and reviewed for any irregularities that need to be discussed with the patient.

**Combination product development**

**PharmTech:** How might trainers be used in combination product development?

**Hawkins (Noble):** Some of the top pharmaceutical companies have realized the value of incorporating realistic trainers into the commercialization and marketing strategy of their new drugs intended for self-administration. It is ideal to start development of a trainer as early in the process as possible—preferably in tandem with combination product development. This gives ample opportunity to collaborate on a variety of conceptual, technical, and logistical requirements regarding trainer design, development, manufacturing, and launch. For example, a pharmaceutical company can determine the precise specifications of the trainer, along with the specific mechanical and smart features they would like it to incorporate.

Finally, the company can help shape the development of a global launch strategy for when the combination product is ready to go to market. With a pharmaceutical company’s success ultimately tied to the reception of each new drug, the availability of a realistic, multisensory training device could contribute significantly to a drug’s reception for both patients and healthcare practitioners.

Successfully launching a combination product can be strengthened by the creation of a robust patient support program that aims to help patients with onboarding and beyond. **PT**

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**Regulatory developments in combination products**

FDA Commissioner Scott Gottlieb has been promoting drug market competition in recent months that includes new guidance documents and targeted advisories to support R&D of complex drugs and combination products. A revised draft guidance discusses studies to evaluate the adhesiveness performance of proposed generic transdermal and topical delivery systems (TDS) products. A second guidance discusses studies to evaluate in-vivo skin irritation and sensitization potential of such treatments. FDA also has issued 235 product-specific guidance documents on the appropriate methods for developing specific generic TDS products (1).

In Europe, the European Medicines Agency (EMA) has pharmaceutical companies concerned after the agency announced it was slowing down work on certain guidelines due to Brexit. The industry has been waiting for a guideline on the assessment of device components in combination products under the European Union’s Medical Devices Regulation (MDR), which requires drug-device components in integral drug-device combinations (DDCs) to be evaluated by notified bodies. The process for this is still unclear, and some companies are worried this guideline delay will affect marketing authorization of integral DDCs, which range from pre-filled syringes to complex electro-mechanical devices (2).

EMA, however, has assured industry that work on the MDR guideline will continue. In an interview with *Pharmaceutical Technology Europe*, an agency spokesperson stated: “EMA is aware of the concerns raised by the industry that came with the introduction of the new MDR, and in particular with Article 117 (requiring an NB opinion on combination products) … Work on seven guidelines which address either an urgent public/animal health need or are necessary to support and facilitate preparation for Brexit or the implementation of new or revised legislation will continue beyond Nov. 1, 2018. This includes the guideline on quality requirements of medicinal products containing a device component for delivery or use of the medical product” (2).

**References**


—Susan Haigney
Transdermal drug delivery is seen as a desirable alternative to oral delivery, says Hayley Lewis, senior vice-president of Operations at Zosano Pharma, which is a pioneer in microneedle therapeutics. Transdermal drug delivery systems (TDDS) include various constructions of patches to be placed on the skin, microneedles applied using devices, and patches that incorporate microneedles, such as Zosano’s product. Pharmaceutical Technology spoke with Lewis about manufacturing considerations for TDDS and about Zosano’s trademarked Adhesive Dermally Applied Microneedle System, which is currently in clinical trials.

Microneedle TDDS
PharmTech: What are some of the advantages of microneedle TDDS?
Lewis (Zosano): For active/assisted TDDS technologies involving microneedles, achieving immediate release in a less-invasive manner through the intradermal route is the major distinguishing characteristic of the technology. In addition, limitations with respect to the molecular weight of the drug are not of concern with this form of assisted transdermal technology. For therapeutic protein and peptide delivery, while intradermal delivery may provide a more advantageous pharmacokinetic profile compared with subcutaneous or intramuscular injections, other tangible patient benefits, such as easy self-administration, less perceived pain, enhanced safety, and ambient temperature stability, are correspondingly essential to make microneedle-mediated TDDS a compelling product concept.

Zosano Pharma has demonstrated the utility of its Adhesive Dermally Applied Microneedle System (ADAM) platform in multiple clinical trials. For example, M207 is Zosano’s proprietary zolmitriptan-coated microneedle patch designed to rapidly deliver the drug during a migraine attack; it is currently in a Phase III clinical trial.

Manufacturing considerations
PharmTech: What are some of the primary considerations for developing and manufacturing TDDS patches?
Lewis (Zosano): A major impediment to overcome in formulating adhesives for TDDS is the difficulty in maintaining compatibility between the API and the adhesive. Adhesive manufacturers should offer formulations with judiciously designed chemistries that will not react with the API or alter its physical properties. In addition, adhesive manufacturers need to fully characterize their adhesives with respect to residual monomers, initiator byproducts (e.g., tetramethylsuccinimide), and any potential degradants. Biocompatibility of an adhesive with the skin is a major concern in the design of any transdermal patch.

The physicochemical properties of the API need to be determined with respect to molecular weight, partition coefficient, melting point, pKa, solubility, pH effects, particle size, and polymorphism. The likelihood of precipitation, particle growth, change in crystal habit, or other API characteristics that may affect the thermodynamic activity from changes in temperature and storage should be evaluated.

In-vitro drug release is an important component of drug product characterization and is routinely used as a quality control test in assessing reproducibility of the drug product manufacturing process. The tackiness of the TDDS also needs to be assessed; typically four tests are generally used to evaluate in-vitro adhesive properties:
- Liner release test: force required to remove the liner from the adhesive prior to application of the patch, to determine the feasibility of removal by the patient
- Probe tack test: ability of the adhesive to adhere to the surface with minimal contact pressure

Drug and adhesive formulation are crucial to the development of microneedle patches.
• Peel adhesion test: force required to peel away an adhesive after it has been attached to the substrate
• Shear test, static or dynamic: the internal or cohesive strength of the adhesive.

Stainless steel remains the preferred substrate used for in-vitro testing as it represents an acceptable alternative to human skin. The advantage of the ADAM technology over traditional TDDS is that the API is not in contact with the adhesive, thus compatibility issues are less pronounced. Furthermore, unlike traditional TDDS, ADAM API is in the solid state, thus concerns with precipitation, particle growth, change in crystal habit, or other API characteristics that may affect thermodynamic activity are obviated. ADAM is packaged in a heat-sealed, nitrogen-purged, and desiccated foil cup, which ensures long-term stability.

**PharmTech:** What variables affect adhesion of the patch to the skin?

**Lewis (Zosano):** A number of factors can impact adhesive performance. The

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### Developing transdermal patches

**McNamara (3M):** Transdermal patches are a non-invasive way of self-administering medication. Because the drug is delivered through the skin, it avoids the gastrointestinal tract, so there are potentially fewer side-effects. Patches offer the ability to maintain a constant therapeutic effect for up to seven days. Transdermal patches also allow for removal of a drug in the event of an adverse reaction.

Not all medications are the right fit [for delivery using a patch]. In order to achieve proper skin absorption and penetration, the API should be non-ionic and be relatively lipophilic to enable partitioning into the lipophilic skin barrier. The molecular weight should be under 500 Dalton, as larger molecules cannot pass through the stratum corneum. The therapeutic dose of the drug should also be less than about 10 mg per day. Finally, FDA has strict standards on elemental impurities in drug substances and delivery methods that must be considered.

When it comes to pairing a drug with a patch, there are many things to consider. What is the release rate of the drug? Does it need to be administered over the course of a few hours, a day, or a week? When the API and adhesive are mixed together, it can speed up the rate at which the drug passes through the skin (because the drug is closer in proximity to the skin), but it can lessen the effectiveness of the adhesive itself. In some cases, the API and adhesive cannot be mixed together, because their material components are simply not compatible, thus requiring an alternative layering structure within the patch.

When it comes to manufacturing controlled substances, there are significant challenges to consider, including regulatory hurdles, supply chain issues, and safety and security concerns. It is important to maintain strict checks and balances in order to properly follow policies and procedures.

We have developed four options for the construction of a patch to ensure the optimized delivery of any given drug based on varying factors, such as the prescribed release rate of the drug and how long the patch must stick to the skin. The differences between these options boil down to how the liners, membranes, backings, and overlay tapes are all layered together. In two of those layering options, the drug is mixed with the adhesive (known as drug-in-adhesive), and in the other two layering options, the drug is in a separate layer of its own.

### Patch adhesion

**PharmTech:** What variables affect adhesion of the patch to the skin?

**McNamara (3M):** Patient skin is the single biggest variable. Everyone has different levels of tolerance and sensitivity to adhesive materials. We run tests to the extent that we can, but until someone tries a patch for the first time, there is no way to know how his/her skin will react to it.

Beyond that, anything that you put into an adhesive can have an adverse effect on adhesion. If the drug and the adhesive are mixed together, the strength of adhesive may be diminished. Conversely, if the drug is not combined with the adhesive, and instead placed into a different layer of the patch, the adhesive will stick to the skin for a longer period of time.

On the manufacturing side, there are a number of things that can affect adhesion. For instance, to maintain high adhesion, the material can’t be too thick or too thin. The processes for laminating and drying the product also play a role.

There are ways to assist adhesion. If a patch itself is not strong enough to stick for the prescribed length of time, overlay tape can be used to help keep it in place. Medical tape can provide for a longer wear period, without affecting the drug delivery. So, when a longer lasting patch is necessary, we incorporate overlay tape into the design of a patch.

### Trends

**PharmTech:** What trends do you see in use or manufacturing of transdermal patches?

**McNamara (3M):** The switch from new patch formulations to generics continues to be a trend that is impacting many aspects of our industry. Most of the major categories of transdermal drugs in the United States have generic forms, and there are now also over-the-counter options competing for consumer dollars. With that trend comes the growing need for increased speed and flexibility in order to compete in a fiercely competitive space.

In the generics world, a successful business model is dictated by three main factors: being the first to arrive on the market, offering the lowest cost option for consumers, and maintaining the quality expected from the brand-name product. Manufacturers of transdermal patches are facing significant price pressure. They must produce a high-value product at a low cost.

We know this reality creates major pain points for everyone in this industry. At 3M Drug Delivery Systems, we’ve recently made significant investments in new high-efficiency transdermal manufacturing equipment to make the process more efficient. Under current market pressures and time constraints, it is more important than ever to prevent malfunctions of equipment and materials, so quality is key. Using lower-cost/lower-quality materials may seem like a smart move, but in fact, it poses a substantial risk.
construction must ensure that all component materials are flexible and the patch comfortably adheres and conforms to a number of application sites. Careful consideration of product geometry avoids uplifting of patch edges. Rounded edges are preferable to prevent patch lifting and to avoid irritation at corners. The product maintains proper adhesion during physical activity and normal exposure to moisture, including sweating, showering, or swimming.

An advantage of the ADAM technology is that wear times are considerably shorter than traditional TDDS. The ADAM patch is only worn for 30 minutes and thereafter removed and disposed. The primary function of the adhesive in the ADAM patch is not to ensure that it sticks to the skin, but rather to ensure that the array of titanium microneedles are attached to the ADAM system components.

PharmTech: What are some of the considerations for manufacturing microneedle arrays?

Lewis (Zosano): With many traditional patch technologies, only a small percentage of drug is actually delivered from the patch reservoir into the skin. In the current environment of cost containment and disposal risks, this is undesirable, particularly for the more expensive, potent biopharmaceuticals. In order to maximize the efficiency of drug incorporation into the patch and to ensure the precision of drug transport to the skin, a coating process has been developed that applies the drug formulation on the microneedles. Manufacturing the ADAM zolmitriptan patch system requires a series of novel processes, including a dip coating technology by placing a minute amount of zolmitriptan formulation on each microneedle. The microneedles are 340 μm in height, 120 μm in width, and 25 μm in thickness. A dip coating concept evolved into a robust coating apparatus engineered to coat a uniform dose in a controlled fashion on the microneedle. It employs a rotating drum to create a liquid drug formulation film with a controlled thickness. Microneedles, moving in the same direction as the rotating drum, are dipped into the film at a controlled depth. Certainly, the mechanical designs and engineering controls and manipulations are essential for coating accuracy and uniformity. The liquid formulation, however, plays an equally critical, if not more important, role. The liquid formulation must be chemically and physically stable during the coating process and should possess adequate properties allowing the formulation to be effectively coated on the titanium microneedles.

Regulatory considerations

PharmTech: What are some of the regulatory considerations for combination products, such as patches?

Lewis (Zosano): Understanding the classification of TDDS products from a regulatory perspective and building the appropriate quality systems and regulatory controls around it throughout development are key to ensuring that the product has the best possible chance of being effective, safe, and approved.

Identifying the performance requirements and uses of all the components within a delivery system is key to setting and managing the controls of the product. In the case of ADAM, the product is regarded, as a single entity combination product, which consists of a device constituent and a drug product. The device and the drug product are made up of several components, and it may be challenging to understand which applicable regulation controls each component, including required tests and specifications, as well as to negate inappropriate regulations and requirements.
In August 2018, Boehringer Ingelheim broke ground on the Solids Launch facility at its production site in Ingelheim, Germany. The facility, which will open in 2020, will develop manufacturing processes for drugs in tablet form. Pharmaceutical Technology spoke with Peter Comes, head of the Factory Solids Launch at Boehringer Ingelheim, about plans for the new facility and what the company views as best practices in scaling up new products and manufacturing processes.

Solids Launch facility
PharmTech: What is the mission and purpose of the new Solids Launch facility? How does it fit into the overall structure of Boehringer Ingelheim’s development and production for solid-dosage drugs?

Comes (Boehringer Ingelheim): The new Solids Launch facility in Ingelheim will focus on launch and industrialization activities for drugs in tablet form. Starting in 2020, 75 employees will start operations, including new production methods for tablet preparations, and manufacture these centrally for all global market launches. Therefore, the deeper mission and purpose of the facility is to industrialize and launch Boehringer Ingelheim’s new chemical entities (NCEs). It allows an early transfer of NCEs from development, approximately four years before launch, industrialization, and early transfer into a routine production network.

Moreover, the Solids Launch facility will be Boehringer Ingelheim’s technology competence center for current and future production technologies for small molecules. It will be the lead site to develop and industrialize modern pharmaceutical manufacturing, for example, in development, test, and implementation of Industry 4.0 tools for the production network.

The facility is an important piece of the puzzle, allowing Boehringer Ingelheim to manage the entire value chain over the long term, from research and development through launch site to routine production.

PharmTech: What are some of the technologies planned for the new facility?

Comes (Boehringer Ingelheim): Fluid-bed granulation, dry granulation, roller compaction, tableting, and film coating are technologies to be implemented. Planned technologies for the future, which are not going to be installed initially, are, for example, twin-screw extrusion and continuous granulation. In addition, we have one train designed as contained equipment to handle higher potent compounds.

Production activities will be controlled using process analytical technology. The new facility will be used to test and to initially implement technology standards for pharmaceutical production. One example is a fully contained production train that will be implemented to handle higher potency compounds.

Beyond pharmaceutical production, the site serves as the lead site to develop and industrialize modern production processes, such as the usage of smart glasses in pharmaceutical production for changeover or remote maintenance. The Solids Launch facility will be used to implement the next generation of electronic batch records, integrating currently independent information technology systems.

Best practices
PharmTech: What are some of the best practices for connecting early development to future manufacturing scale-up?

Comes (Boehringer Ingelheim): The former philosophy was to adapt production processes to existing manufacturing equipment. This procedure...
In bio/pharmaceutical manufacturing, monitoring the bioburden of raw materials, intermediates, drug substances, formulated drug products, and processing environments is essential for ensuring patient safety. Successful bioburden monitoring requires knowledge of both the quantity and identity of detected microbes. The level of information and extent of microbe characterization, and thus the testing protocols, required depend on the specific sample and situation. In cases of potential contamination, knowledge of the identity of a contaminant can help determine its source and thus an appropriate course of action. It is essential, therefore, to implement a microbial identification strategy as part of an effective microbial control program.

Microbial identification is an important and often overlooked component of bioburden monitoring programs, according to Phil Tuckett, study director at Nelson Laboratories. The intent is to characterize microbes to differentiate one type from another. Identification allows placement of the microbe, depending on the required level of identification and the type of testing employed, into a specific family (genus), species, and/or strain.

Microbial identifications can be used to provide a platform for thorough investigations, such as for determining the nature of specific contamination events, according to Poonam Bhende, assistant manager at SGS Life Sciences. Microbial identity determination can also be used in a broader manner to provide a rough estimate of the bioburden in a dose of product as an indication of its sterility.

“It is important to understand not only the numbers of microorganisms present in a product, but also the types of microorganisms they are. Particularly with regard to bioburden reduction strategies, the identity of a microorganism can dictate the best practice for eliminating it,” says Tuckett. Indeed, Bhende notes that through detailed and accurate microbial identification, it is possible to narrow down the source of contamination and take appropriate measures to mitigate the risk for future contamination.

Many options
There are several methods available for microbial identification. They are generally classified as phenotypic or genotypic techniques.

Phenotypic testing provides data on the physical properties (i.e., morphology, reaction to different chemicals, behavior under certain conditions) that are indicative of a microbe’s genus and in some cases species. Phenotypic methods, which focus on outward characteristics of an organism—appearance, staining characteristics, biochemical utilization, metabolic requirements, protein analysis—are important components of the microbial characterization level. Given enough of these tests, along with a high level of expertise, a genus/species ID may be obtained,” observes Tuckett. Currently, these methods are most widely used because they tend to be lower in cost and easier to implement. They are, however, generally culture-based and growth dependent, and results can vary with the media and growth conditions that are used. In addition, because many phenotypic tests involve studying the response to treatment with biochemical reagents, repeatability can be an issue.

Automated systems have been developed to overcome some of these limitations, including Fourier-transform infrared spectroscopy, matrix-assisted laser desorption ionization–time of flight (MALDI–TOF) mass spectrometry, and flow cytometry.

The industry is, however, moving toward genotypic identification methods due to the growing number of species that are being described every year, according to Tuckett. Genotypic methods involve analysis of the genetic makeup.

Microbial Identification Strategies for Bioburden Control

Cynthia A. Challener

Microbial identity data can be critical for determining contamination sources.

The value of identification
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The first thing to consider is what level of expertise because appearances can be variable and many characteristics of microorganisms change over time. Given the inherent subjectivity of some of these tests, Tuckett strongly recommends that genus/species identification be performed for at least the overall three to five most common organisms.

In situations where action/alert levels are exceeded or when contamination events are encountered, genus/species level identification is more appropriate. “Since microbial identification is used to understand the source of contamination, it is important for the identification method to give an accurate species identification in order to implement appropriate corrective actions and preventative actions (CAPA). Implementation of the appropriate CAPA will prevent the re-occurrence of microbial contamination and reduce the risk of quality issues in the manufacturing process,” Darker comments.

Species identification is also an essential part of testing for objectionable organisms (United States Pharmacopeia 62 testing), according to Tuckett, because mere characterization can sometimes be insufficient to rule out specific species.

At SGS, most clients ask for species-level identification. "Species-level identification helps us to eliminate the risk of an antibiotic-resistant pathogen becoming prevalent if a new strain is observed that cannot be eliminated through cleaning by disinfectant. Additionally, seasonal change can see a change in bioburden levels which need to be identified,” says Bhende.

When investigations are being conducted to determine if multiple contaminants are of the same source, bacterial strain typing is necessary. “This testing reveals if different isolates come from the same strain or source, which cannot be determined from species level identification methods,” Tuckett explains.

Hallmarks of effective strategies
An effective microbial identification strategy, according to Darker, results in the determination of the root cause of the contamination. “In essence, if CAPA has been put in place and it mitigates any further risk to product quality and patient safety, then the microbial identification strategy was effective,” she states.

For Tuckett, an effective microbial identification strategy is one that provides meaningful data pertinent to the given situation and draws upon sufficient resources to ensure the identification is as accurate as possible. “The basic principle behind microbial identification is comparison of the characteristics of an unknown organism to those of a known organism. The more that is known about the known organism, the better the comparisons can be. When genotypic data [are] analyzed, [they are] generally compared to a library or database of known DNA sequences and [are] therefore only as accurate as the database [they draw] upon. An extremely limited database may provide inaccurate identifications,” he explains. In addition, methods based on automated identification software may be inadequate for the intended use if a high number of “unidentified” results are obtained.

An ineffective strategy is also one for which a CAPA cannot be implemented to stop the reoccurrence of contamination by an identified microbe, according to Bhende. Therefore, as with bioburden and environmental monitoring programs, continuous evaluation and assessment of microbial identification strategies are essential. “As compendial requirements change, and as new technologies become available, identification procedures should be reevaluated to ensure they are sufficient for their intended purpose. If a specific identification method doesn't yield adequate results, alternate methods should be considered,” asserts Tuckett.

For clients of SGS, Bhende also recommends for critical microbial identification applications the establishment and maintenance of a database logging the trending data for locations and accurate identifications. “This information can be used to identify early on any potential patterns of contamination that need to be addressed,” she says.
Contract Organizations Expanding in Autumn

Susan Haigney

CMOs and CDMOs made investments in new and expanded facilities and services in the last quarter of 2018. Contract manufacturing organizations (CMOs) and contract research and development organizations (CDMOs) invested in expanded facilities and services in late 2018. The following are some recent investments by CMOs and CDMOs.

New and expanded facilities
Thermo Fisher Scientific announced the opening of its new business center and biorepository in Frederick, MD, in October (1). The center, which has been expanded by more than 190,000 ft² and will serve as the North American hub for the company’s life-sciences business, is the largest building on the Frederick campus and has more than 80 employees. The expansion includes another 22,000 ft² to accommodate future growth and advancements in automation, bringing the company’s total investment in the facility to nearly $10 million.

The expansion also adds a 77,000-ft² facility to house a cryo-innovation center and National Cancer Institute’s repository for clinical trials. Another 15,000 ft² have been reserved for future expansion, the company reports.

The cryo-innovation center will be a future third-party logistics site to support clinical trial and commercial cell and gene therapy, employing 20 people and representing an investment of $5 million. The site will consolidate several smaller facilities, making it a center of excellence for clinical and academic research sample storage.

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The facility supporting the National Cancer Institute will serve as a central biorepository to support oncology clinical trials. This represents a $2-million investment and employs more than 15 people.

Development and clinical manufacturing company Velesco Pharm acquired a new facility in Wixom, MI, that expands and enhances its formulation and analytical R&D capabilities (2). The acquisition and fit-out of the new facility double the company’s formulation and analytical laboratory space. The increase in capacity expands its research and current good manufacturing practice (CGMP) services, including formulation development, analytical method development/validation, release and stability testing, and CGMP clinical manufacturing. The move to the expanded facility will occur before the end of 2018, the company reports.

Quotient Sciences, a drug development services organization, has expanded its operations in the United States with the opening of a state-of-the-art, 45,000-ft² facility located in Garnet Valley, PA (3). The $15-million investment will create a center of excellence for early-phase formulation development and clinical trial manufacturing. The site will focus on developing small-molecule oral drug products, supporting development programs from the preclinical stage through to clinical proof-of-concept. The new facility is also designed to handle both potent and non-potent products with six high-potency GMP manufacturing suites. The company reports that scale-up to late-phase manufacturing and commercial product supply will continue at Quotient’s nearby Chelsea Parkway facility.

The expanded formulation development, analytical, and manufacturing capabilities enable biotech and pharmaceutical companies to access the company’s Translational Pharmaceutics programs working under an investigational new drug (IND) application. The company reports that this approach integrates real-time adaptive manufacturing and clinical research. Drug products manufactured at the
Garnet Valley facility can be rapidly supplied into global patient trials and clinical pharmacology units, using tailored batch sizes and flexible dose adjustments, according to the company.

Cambrex Corporation will establish a center of excellence for API clinical supply and process development at its site in High Point, NC, the company announced on Sept. 25, 2018 (4).

The company will acquire its currently leased 35,000-ft² facility and an adjacent 45,000-ft² building, which will be fitted out with kilo-scale and pilot-scale vessels, continuous reaction production, and laboratories for chemistry, engineering, and analytical development. The purchase of the current and adjacent facility is in response to growing customer requirements for clinical supply manufacturing and analytical and chemical development. The center will also focus on the development of new technologies, innovative chemistry, and engineering solutions as well as expertise in technology transfer to commercial scale.

The facility produces complex APIs and intermediates requiring multi-step synthetic processes in batch sizes from milligrams to 100 kg in support of clinical trials from Phase I through to Phase III. The site is licensed with the US Drug Enforcement Administration (DEA) to manufacture Schedule II to Schedule V controlled substances.

**New services**

SGS, a bio/pharmaceutical, analytical, and bioanalytical contract solutions provider, announced on Oct. 23, 2018 that it is adding new in-vitro toxicology services at its Mississauga, Canada laboratory (5). The investment includes an expansion of existing cell/tissue culture capabilities, flow cytometry, and mass spectrometry facilities, along with the introduction of high-throughput screening, automation, and multiplexing technologies such as the Meso Sector S 600 for biomarker analysis.

The company’s investment in instruments and expansion of the laboratory’s capabilities will allow clients to establish the toxicological profiles of bio/pharmaceuticals, medical devices, cosmetics, and chemicals. The new suite of services covers more than 50 analytical techniques, including dermal and ocular toxicity, cytotoxicity, genotoxicity, carcinogenicity, phototoxicity, endocrine disruption, hepatotoxicity, and cardiotoxicity. The new service offerings will be available under both R&D and good laboratory practice (Organization for Economic Co-operation and Development, FDA Part 58) study conditions.

Almac Diagnostic Services, which specializes in biomarker driven clinical trials, has added an Illumina NovaSeq 6000 sequencer to its range of next-generation sequencing capabilities, which include DNA and RNA sequencing offerings (6). The company states the new equipment will allow for larger sample runs, greater read depth, and faster speeds, and will reduce sample turnaround times and increase variant detection quality and accuracy. Almac has also invested in informatic infrastructure and high-speed uplinks to cloud-based providers to support the new capacity.

The company will now be able to sequence transcriptions of up to approximately 384 samples per run in as short as 36 hours. Scalable throughput and flexibility for any sequencing method, genome, or scale of project will now be available to the company’s clients. The company’s customizable solution allows its clients to tailor their diagnostic requirements across multiple platforms and chemistry options.

**New investments**

ADC Biotechnology (ADC Bio) has secured additional funding of $3.18 million (£2.5 million) from existing investors and company management to ensure the achievement of specific business goals within the company’s overarching corporate strategy.

“We are delighted to have obtained this additional injection of funds that will be used to support the company’s strategic aspirations, including conceptual design of a downstream formulation and filling operation to complement our existing bioconjugation operations at the Deeside facility. We are also looking to fully exploit our core Lock-Release technology to create a transformative manufacturing paradigm that will significantly streamline ADC manufacturing supply chains,” said Charlie Johnson, CEO of ADC Bio, in a company press statement (7).

**References**

was unfavorable as it led to significant efforts concerning the ‘re-development’ of production processes and validation activities. Boehringer Ingelheim is currently implementing its ‘Supply Network Strategy,’ which describes technology standards from development to the launch side and again to routine production with regard to technology and equipment. Preferably during transfer, the manufacturing scale will be maintained. If necessary, scale-up will be performed at routine sites, including internal and external sites.

PharmTech: Can you describe some best practices for analytical testing and quality control testing in a scale-up project?

Comes (Boehringer Ingelheim): With regard to best practices, it is important to mention the use of standardized quality control equipment, which is currently being rolled out at the relevant locations. In addition, we have a dedicated organization for transfer activities and a global team that coordinates the respective transfer activities. This (coordination) helps enormously to make processes smoother.

Facility construction
PharmTech: In 2016 and 2017, the company constructed the “Diabetes Factory” in Ingelheim, which will develop and launch innovative antidiabetic agents. How will what was learned from that project be applied to the Solids Launch facility?

“[The Solids Launch facility] allows an early transfer of new chemical entities from development.” —Peter Comes

Comes (Boehringer Ingelheim): The Diabetes facility was built to meet additional market demands. The highest priority for the facility was time. Only 18 months passed from the starting point of the planning phase until the first products were produced. The pure construction time was 12 months. A key element to realize the tight construction timelines of the facility was the stringent usage of BIM (building information modeling). BIM technology will also be used to plan and build the Solids Launch facility.

Layout wise, the new Solids Launch facility consists of two trains allocated in separated compartments, which reflect the Diabetes facility’s production train with a central compartment for dispensing, cleaning, and storage. The design philosophy of the Solids Launch facility is similar to that of the Diabetes facility. The outer shell provides maximum flexibility in the allocation of production facilities. The shell-in-shell design and a technical area accessible from the outside allow individual production rooms to be modified without affecting the rest of the plant.

The schedules of the Diabetes facility could be optimized by mapping existing production facilities on site to avoid lengthy validation and stability activities. The same philosophy is applied at the Solids Launch facility, with the use of standardized manufacturing facilities from development through commissioning, to routine production facilities.

Quality: Technology Transfer — contin. from page 25

Szczesniak: The first step is to understand and analyze your own company’s limitations in terms of specific knowledge and experience for the project at hand. Then fill in your knowledge gaps with the appropriate consultants and the CDMO. A key component of your relationship with the right CDMO should be education: their technical leads should be able to explain not just what they are doing, but why, in the same way that they should be able to explain to an auditor or FDA investigator what they have done, and why.

There should be a continual feedback loop of review and information to the client as the project progresses. Your knowledge and understanding of your product should grow throughout its development life. Look for a CDMO that can communicate technical and scientific information, and consider this an important part of the contract partner selection process.

Beyond that, evaluate the progress of your project against its development strategy. Work completed needs to be considered in the context of your overall goals. It is important to conduct gate-keeping reviews before starting significant steps, such as the manufacture of registration batches or validation batches, to verify that the project is ready to advance.

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all the batch records completed by the other operators to determine if the product is still acceptable. Admittedly, this is a simplistic example, but it certainly exemplifies the importance of opting to perform a complete and thorough investigation over meeting an artificially imposed time frame. Explaining to an inspector during an audit that you didn’t perform a thorough investigation because you needed to meet an arbitrary time frame is not a position you want your company to be in. You also don’t want to explain why you closed an investigation to meet the time frame and then felt compelled to reopen it after the batch was released because you had concerns about its conclusions.

Quality over brevity
The other element that needs to be addressed is that of the prevalent culture existing in the organization. It is good to set a time goal for performing investigation, thus ensuring their timely completion. It is not acceptable to have the time frame be the driving force behind the investigation. Management needs to emphasize their commitment to having thorough investigations as opposed to incomplete investigations that meet the self-imposed time frame. It is ideal when an investigation is completed and a true root cause identified in the specified time frame but, if that is not achievable, management needs to be clear that they prefer the identification of the true root cause over the rushed investigation that merely checks the box for completion in a timely manner. Without this management commitment, the premature closing of investigations will likely continue.

Investigations need to focus on determining root cause in a timely manner. The length of time it takes to complete an investigation depends on the complexity of the investigation. The primary driver for avoiding compliance and data integrity risks concerning investigations is arriving at a root cause in a timely manner. This allows you to be confident in presenting your investigations during inspection and avoiding unnecessary scrutiny when the investigation is rushed and a conclusion is reached prematurely.

References
1. FDA, 21 CFR 211.22(a), Current Good Manufacturing Practice for Finished Pharmaceuticals, Responsibilities of Quality Control Unit, Sept. 29, 1978.
A required time frame should not be the driving force behind root-cause investigations, says Susan Schniepp, executive vice-president of Post-Approval Pharma and Distinguished Fellow, Regulatory Compliance Associates.

Q. I have just been promoted to be in charge of investigations for my company. Our standard operating procedure (SOP) requires us to complete investigations in 30 days. Depending on the nature of the investigation and to meet the SOP requirement, I have started to close investigations at the 30-day time point even though I think the investigation might not be complete. Sometimes I have had to re-open investigations because the problem recurs, confirming that the investigation was not completed. Do I have a compliance risk if I continue with this practice?

A. The short answer is yes, you have a compliance risk. You probably also have a data integrity issue and a quality culture issue to accompany your compliance risk.

There is no time element associated with conducting investigations. Thirty days is an arbitrary number pharmaceutical companies impose on themselves. The US Code of Federal Regulations states “… if errors have occurred, that they have been fully investigated” (1), and “Any unexplained discrepancy … shall be thoroughly investigated, whether or not the batch has already been distributed” (2). Europe’s EudraLex also addresses investigations by stating, “An appropriate level of root cause analysis should be applied during the investigation of deviations …” (3). None of these citations indicate a time for completion of an investigation. What they do imply is that investigations need to be thorough and determine root cause. In some cases, the investigation and root cause can be easily determined in the defined SOP time frame of 30 days. In other cases, the investigation may be more complicated and could exceed the time frame requirement of 30 days. To address this potential discrepancy, your SOP should allow for investigation extensions. The length of the extension request should be made based on the complexity of the investigation.

Data integrity problems

When an investigation is rushed, the organization leaves itself vulnerable. Suppose, for example, you have a second shift manufacturing operator who continually forgets to sign a step in the batch record for a specific product. This operator is the only one who seems to have this issue. Your initial investigation into the first occurrence of the issue determines a root cause of human error. Because the operator works on the second shift, it is inconvenient to interview him directly, so you rely on the word of his supervisor that this was just a case of human error. You decide to retrain the operator on the proper use of filling out the form and skip the operator interview in order to complete the investigation and perform the retraining in the allotted 30-day time frame.

A few weeks later, the same operator makes the same mistake. You review the previous investigation, arrive at the same conclusion, and perform the retraining of the operator emphasizing the importance of correctly filling out the batch record. This scenario repeats itself 10 times over the course of four months. You finally decide to question the ability of the operator to do the job correctly and bring your concerns to management.

Your boss asks if anyone has interviewed the operator directly to find out why he is having this issue with the batch record. You say no, that you have relied on the opinion of the supervisor. The boss recommends you interview the operator before demoting him.

When you talk to the operator, he informs you that in order to sign the batch record when it needs to be signed, he needs to exit the aseptic core, degown, sign the batch record, and regown, leaving the product unattended during that time. The operator tells you he chose to stay with the product and sign the batch record later but sometimes forgot after the manufacturing run. In this simple exchange with the operator you realize that the root cause of the repeat deviation is not a result of human error but a result of poor process flow.

The question you need to address now is how were other operators handling the situation? By not taking the time to perform the initial investigation thoroughly, you have created a data integrity nightmare because you now need to review...
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