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FROM THE EDITOR

Pharma Facilities Still Have a Lot to Learn

FDA’s annual manufacturing report card shows more quality compliance is needed.

REGULATION & COMPLIANCE

REGULATORY WATCH

FDA Advances New Approach to Drug Quality Assessment

CDER’s KASA program seeks manufacturer data on drug attributes and risks to inform oversight.

ASK THE EXPERT

Quality Agreements and Out-of-Specification Investigations

A good working relationship between sponsor and contractor will become invaluable when an OOS occurs, says Susan J. Schniepp, executive vice-president of post-approval pharma and distinguished fellow, Regulatory Compliance Associates.

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As schools in the United States close for the summer break, student grades serve as a measure of how well teachers shared knowledge, how well students understood and retained that information, and how the school, as a whole, performed this year.

FDA recently issued a report card of the bio/pharma industry’s manufacturing quality performance, which provided insight on how well manufacturers and regulatory authorities executed their responsibilities, and lessons learned for future improvements.

The Report on the State of Pharmaceutical Quality (1), issued in May 2019 by the Office of Pharmaceutical Quality in FDA, Center for Drug Evaluation and Research, assessed the ability of pharmaceutical manufacturers to deliver quality pharmaceutical products to the US market during fiscal year 2018. The report analyzed product recalls, quality defect reports, drug shortages, and application state (e.g., submissions, approvals, refuse-to-file, refuse-to-receive, and complete response letters) as a basis for its analysis.

Site report card
The report examined manufacturing site data by geographic region, therapeutic category, application type, and manufacturing sector. FDA issues a site inspection score—on a scale of 1 to 10 with a higher number indicating greater compliance with current good manufacturing practices—based on FDA quality inspections over the past 10 years.

The number of sites in FDA’s site catalog—4676 at the end of FY2018—needs some clarification. Of the total sites in the catalog, 42% manufacture “no application” products, such as over-the-counter products, monograph, unapproved, or homeopathic products. The remaining 58% of sites manufacture application drug products (e.g., new drug application [NDA], abbreviated new drug applications [ANDA], biologic license application, etc.) and nearly half (46%) of these sites manufacture both NDA and ANDA products.

The report noted “volatility” in the site catalog in the past year; the agency removed from the catalog “a large number” of sites in India, China, and South Korea in FY2018 because they did not make products for the US market and, therefore, did not have to be registered with FDA. The need to purge manufacturing sites from the list indicates “a lack of understanding of the registration and listing requirements,” FDA noted in the report.

The data also show shifts in the types of site registrations. FDA reported a 32.8% net increase in the number of packaging and labeling sites—suggesting an increase in outsourcing of these functions. In addition, there was a 29.7% net increase in the number of “no application” sites and a net loss in the number of NDA sites.

Less than 40% of the drugs for the US market are manufactured in the US; India (12%) and China (11%) are the two largest offshore suppliers. FDA also noted that a small number of sites manufacture a large number of listed products; the number of products manufactured at a site is a risk factor used in prioritizing the need for surveillance inspections. In the US, three sites—two of which make homeopathic products—account for 9.5% of all products listed by all US sites. The number of listed products manufactured by the top three sites in China (11.2%) and India (12%) are even higher.

Inspections and grading
In FY2018, FDA conducted 1346 drug quality inspections, covering less than one-third of sites in its catalog; more than half of the inspections were outside the US. The average inspection score of 7.5 for FY2018 was down slightly from FY2017 (7.7). Sites in the European Union (7.9) and the US (7.7) scored higher than average; sites in China (7.0), India (7.0), and the rest of the world (7.2) were lower than average. Statistical differences were also noted in application areas, with sterile non-application products as one of the lowest performing.

FDA noted “… some trends highlight opportunities for increased outreach to, surveillance of, and enforcement of certain markets,” indicating that for regulated drug manufacturing, school is never out.

Reference
2019 PDA Rapid Microbiological Methods Workshop

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- **Andrew Hopkins,** *AbbVie, Inc.* and formerly with MHRA
- **Haijing Hu,** PhD, CDER, FDA
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Cleanroom Monitoring Software Solution

Particle Measuring Systems’ new Pharmaceutical Net Pro cleanroom monitoring software for data and collection management and automation offers flexible integration options and intelligent features such as facility mapping, alarming, reporting, and recipe-driven sampling.

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The software is used with the company’s FacilityPro Processors, which connect directly to environmental sensors, including viable air samplers and non-viable particle counters, temperature/humidity sensors, human-machine interface stations, as well as light towers for visual alarm indication. Built on an industrial automation architecture, the software meets all relevant regulatory requirements, including 21 Code of Federal Regulations Part 11 for data integrity and GAMP 5 Category 4.

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New media mixing steps automate the creation of media blends, eliminating the need to pre-mix. Rapid vessel drain functionality for automated cell passaging and media exchanges in the microbioreactors supports cell and gene therapy applications. A new culture station design provides lower stirrer speed control suitable for more sensitive cell lines.

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As part of its ongoing efforts to ensure the availability of high-quality medicines, FDA’s Center for Drug Evaluation and Research (CDER) is rolling out a new system to enhance the evaluation of prescription drug attributes, risks, and control strategies. The Knowledge-aided Assessment and Structured Application (KASA) initiative aims to improve the efficiency, consistency, and objectivity of regulatory quality assessment by collecting structured data on drug substance, product design, and manufacturing process to better assess inherent risks and how they are controlled. CDER’s Office of Pharmaceutical Quality (OPQ) is piloting the program first for abbreviated new drug applications (ANDAs) for generics, with the aim of rolling out the system to generic solid oral dosage forms by year-end. Next will come generic liquids and injectables, followed by new drugs and biologics.

With more ANDAs and new drug applications (NDAs) filed each year, many involving complex therapies, and increasingly tight assessment time frames for approval set by user fee programs, CDER officials are looking for ways to evaluate submissions more expeditiously and effectively. This new approach asks manufacturers to file structured applications that present key data on product attributes, as opposed to lengthy, text-based narratives. The aim is for OPQ staffers to perform computer-aided analyses that support benefit/risk assessments for comparison across products and facilities. Under development for almost two years, the KASA initiative became more visible when it was discussed publicly and gained unanimous support at the September 2018 meeting of FDA’s Pharmaceutical Science & Clinical Pharmacology Advisory Committee.

CDER and OPQ leaders presented more detailed information on KASA at the April 2019 PQRI/FDA conference on Advancing Product Quality in Rockville, MD (1). KASA aims to provide a structured assessment of an application that summarizes key information and “minimizes text-based narratives,” explained OPQ Deputy Director Lawrence Yu. Advances in information technology not only generate more information on key quality attributes, Yu pointed out, but also allow for a faster, more complete assessment. He directed manufacturers to an article outlining the KASA program in the International Journal Of Pharmacaceutics: X for further information on the program and its approach (2).

Similarly, at the April 2019 CMC Workshop sponsored by the Drug Information Association (DIA), Geoffrey Wu, associate director of OPQ’s Office of Lifecycle Drug Products (OLDP), described how the KASA initiative will capture and manage knowledge of drug product quality to establish a product risk control strategy for lifecycle management. This approach will avoid inconsistent application of quality standards and help prevent shortages and quality failures of marketed drugs. KASA also will assess manufacturing risks and controls in order to “flag the potential need for a pre-approval inspection based on multiple factors and complexities using standardized risk thresholds,” Wu noted. This will involve examining the control strategy for the manufacturing facility, including site inspection history, based on a standardized assessment of risks compared across products and facilities.

The KASA initiative aims to improve the efficiency, consistency, and objectivity of regulatory quality assessment.

**FDA Advances New Approach to Drug Quality Assessment**

**Jill Wechsler**

CDER’s KASA program seeks manufacturer data on drug attributes and risks to inform oversight.
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Wearable and smart devices allow user-friendly subcutaneous drug delivery.

The trend to self-administered, home-based, subcutaneous drug delivery is creating a need for drug-device combination products that are easy to use correctly and designed with patients in mind. Patients may be familiar with prefilled, handheld autoinjectors or pens. Another type of device, not as familiar today but perhaps soon to see broader use, is the wearable autoinjector, which is attached to the skin to inject a larger volume dose over a matter of minutes, compared to seconds for the smaller dose of a handheld injector. The increasing use of biologics that must be delivered in larger-volume doses is creating a growing need for these larger-volume, wearable autoinjectors, which may also be called patch injectors, large-volume body injectors, on-body delivery systems, or wearable bolus injectors (WBIs).

New device platforms
Choosing a wearable injector rather than a handheld injector depends on the injectable volume and injection frequency, says Ian Thompson, vice-president of business development at Ypsomed Delivery Systems. “We believe the key applications for patch injectors will be in the 3–10 mL space for monthly or quarterly autoimmune or immuno-oncology therapies,” he notes. Ypsomed is developing YpsoDose as a prefilled, ready-to-use, patch injector for antibody-based drugs in the range of 3–10 mL (see Figure 1). Functional devices for testing are available, and the company is engaging in feasibility trials with pharma companies, says Thompson.

Using platform technologies that can be easily customized for multiple therapies is important for manufacturing cost-efficiency, which is particularly important for drugs that target smaller patient populations and thus have low annual quantities, notes Thompson. Ypsomed produces devices for multiple products and customers from the same tooling and equipment. In addition, the electromechanical drive system is programmable for different viscosities or fill volumes. This drive system ensures consistent flow rates, which allow reproducible injection times, and the electronic circuitry is already in place to provide connectivity. The devices are designed to hold standard, 10-mL glass cartridges that are filled in a ready-to-fill tub format.

Sorrel Medical is developing single-use, prefilled wearable injectors in configurations ranging from 1–20 mL. “The 3-mL device configuration has been fully verified and validated and is available for performing feasibility testing by our pharmaceutical partners,” says Andrei Yosef, CEO of Sorrel Medical. “The 20-mL device has working prototypes available. The other configurations are in the earlier stages and can be developed to commercialization with a partner.” Yosef notes that all the devices are based on the same pumping mechanism, with slight modifications to the outer shelling to accommodate different sized primary containers. Using a platform solution lowers risk in development and commercialization, adds Yosef.
Impact of New FDA Guidance on Bioanalytical Testing on Drug Development

ON-DEMAND WEBCAST  Aired May 30, 2019

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EVENT OVERVIEW:

In this webinar, learn how the FDA Bioanalytical Method Validation Guidance (May 2018), the FDA Immunogenicity Testing of Therapeutic Protein Products (January 2019), and the February 2019 draft International Conference on Harmonisation (ICH) Bioanalytical Method Validation M10 guidelines have changed or are poised to change the landscape of outsourcing bioanalysis to support drug development. Additionally, the webinar will cover gaps in bioanalytical method validation guidance to support drug development most notably flow cytometry support of gene therapies.

The webcast will highlight the areas of each guidance that indicate a change of thinking from previous documentation provided by the agency. Experts will discuss the practical side of execution of these updated parameters, where appropriate, and the impact the documents will have on the scope and timeline for outsourcing of bioanalytical analysis.

Key Learning Objectives

- What is new in FDA’s May 2018 Bioanalytical Method Validation Guidance?
- What is new in FDA’s January 2019 Immunogenicity Testing of Therapeutic Protein Products?
- What is new in the February 2019 draft of the ICH Bioanalytical Method Validation M10 guidelines?
- What actions should bioanalytical testing labs take to adapt to these new guidelines?

Who Should Attend

- Pharmaceutical and biopharmaceutical industry CEOs, directors, and scientists who are decision makers within their companies and individuals who outsource bioanalytical to CROs

Presenters

Franklin Spriggs
Director, Biopharmaceutical Services
KCAS Bioanalytical and Biomarker Services

Marsha Luna
Director, Pharmaceutical Services
KCAS Bioanalytical and Biomarker Services

Stephanie Bull, RQAP-GLP
Quality Assurance Team Lead
KCAS Bioanalytical and Biomarker Services

Moderator

Rita Peters
Editorial Director
Pharmaceutical Technology

For questions contact Martha Devia at MDevia@mmhgroup.com
Subcuject is developing a platform for prefilled WBIs to deliver 1–10 mL of drug using an osmotic pump, which is a fully mechanical drive, without electronics. “Osmosis can create a high drive pressure and it is, therefore, not a problem with high viscosities or high tissue back pressure, which can be a problem with electromechanical devices. The injection flow rate is around 1 mL per minute for viscosities up to more than 50 cP,” explains Jesper Roested, CEO of Subcuject. Eliminating the electronic component also eliminates the limitations of battery life in cold storage conditions and reduces the environmental impact of disposal, he says. The company is currently testing performance of functional device models, and the device is expected to be ready for regulatory development by the beginning of 2020. The WBI is designed to have low cost of goods, and assembly and filling is straightforward, says Roested. It is also designed to promote uncomplicated development at pharma companies by using a standard glass cartridge with a plunger of standard material.

The enFuse On-Body Infusor from Enable Injections, shown in Figure 2, is being developed as a device platform for volumes from 5–50 mL, says Matt Huddleston, Enable Injections executive vice-president and chief technology officer. A unique aspect of the technology is the use of a constant-pressure design using an elastomeric pump, rather than a constant-flow design using an electromechanical pump. “This design allows the enFuse to automatically adapt to the injection site back pressure, and it is hypothesized to potentially alleviate infusion site leakage and pain,” notes Huddleston. The company received a US patent in March 2018 for its expandable elastomeric bladder and infusion cannula system, and additional patent applications are pending in the United States and other countries. Apellis Pharmaceuticals is conducting human clinical trials using enFuse technology to deliver its immunotherapies, and biopharmaceutical company UCB entered a development agreement with Enable Injections in November 2018 (1).

West’s SmartDose technology platform (see Figure 3) is an on-body infusor that uses a Daikyo Crystal Zenith cartridge and a Flurotec-coated piston containment system. A combination product from Amgen for a single, monthly dose of Repatha (evolocumab) using West’s SmartDose technology was approved by FDA in July 2016 (2). In January 2019, scPharmaceuticals announced that it had completed preliminary feasibility studies of its Furoscix (furosemide) with the SmartDose Drug Delivery System and was moving forward with development in anticipation of filing a new drug application in 2020 (3). West also announced a collaboration with fill/finish provider Swissfillon, to provide bio/pharma customers with clinical fill/finish capability with the SmartDose technology (4).

Primary container design
Most wearable injectors are designed to use conventional primary containers. A new development program from SCHOTT is being developed as a device platform for volumes from 5–50 mL. The move to self-administration at home rather than in a clinic makes communicating information to patients crucial. Devices designed for self-injection can incorporate “smart” sensors and mechanisms to communicate information from the device to the user. Furthermore, wearable injectors can be connected through the Internet, typically using near-field connectivity (NFC) or Bluetooth, to communicate information through a smartphone or other connected device to a patient or to others, such as their medical team.

On Sorrel Medical’s devices, for example, smart sensors “include air and occlusion detection, needle position, ensuring the primary container is in place, and on-body detection, in addition to a series of internal system checks,” says Yosef. In addition, Sorrel’s devices have integrated NFC and Bluetooth connectivity.

In the enFuse device, a gauge and the button mechanism give active feedback to the patient for delivery progress and end-of-delivery cues, says Huddleston. “Beyond this, an option in development for connectivity will be capable of interfacing with smartphone applications to give information such as the delivery status of the device and the patient,” he adds. “Connectivity could potentially improve patient compliance, verify proper device function, and increase patient safety by identifying possible risks.” Management of confidential patient data, however, is a challenge, and connectivity to a healthcare provider or other party can raise concerns about data privacy.

“Both pharmaceutical companies and device manufacturers are aware of the
vast potential in having data from connected drug delivery devices, and how it may be utilized to benefit various patient populations,” agrees Yosef. “We believe the question of how that data will be used is one that must be had with each individual pharmaceutical partner based on the molecule, the indication, and the patient population.”

Connected devices are being developed for combination products besides wearable injectors. For example, Haselmeier is collaborating with Common Sensing to develop a smart, disposable injector pen platform. Haselmeier’s subcutaneous drug delivery injection systems for self-administration will be combined with Common Sensing’s Gocap injector monitoring technology to record the time and amount of every injector dose, along with other information, such as storage temperature, says the company (5). Initially the monitoring cap will be an on, replacement cap, but is intended to eventually be an integrated device, says Paul Jansen, Haselmeier advisory board member. “Initial products are expected to be focused on clinical trial use. In this environment, patients are engaged and motivated to collect data,” notes Jansen.

Connected devices are ideal tools for disease management, says Sai Shankar, vice-president, Global Digital Healthcare Systems, at Aptar Pharma, which offers both add-on and integrated connected devices for several different delivery routes. “They provide real-time analysis of dose adherence and patterns of dose administration, and they are potentially diagnostic tools to assess patient health and potential exacerbations.” Although the initial cost may be a concern, Shankar believes that the cost of connected devices will come down as increased adoption results in higher volumes. A key challenge for manufacturing connected devices is managing the need for manual assembly of early-stage, low-volume devices as well as the need for automated assembly for higher volumes, he notes. Securing the supply chain for electronic components is crucial, adds Shankar. Selecting known suppliers with medical-grade quality components, dual-sourcing components where feasible, and understanding the total cost of supply are key considerations.

Finding manufacturing efficiencies such as using automation or standard parts (e.g., electronic chip or Bluetooth module) will be important for bringing down the cost of connected products, agrees Jansen. Another challenge is ensuring the electronics and software are compliant, including testing for data security and understanding and minimizing the risk of software bugs. Managing software updates can also be a challenge. “Pharma companies should be prepared for the unique challenges of being accountable for connected products,” Jansen says.

References

Developers of drug-device combination products should use human factors (HF) studies to ensure that the product can be used effectively and safely and “eliminate or mitigate patient adverse events and medication errors attributable to use-related errors” (1).

“Human factors engineering (HFE) studies are not a ‘check the box’ activity to meet submission requirements,” says Stefanie Johns, Enable Injections associate director of Regulatory Affairs. “Complete response letters for drug-device combination products are most frequently a result of HFE deficiencies. It is up to the marketing application holder to demonstrate safe and effective use of the drug-device combination product by the intended users within the intended use environments. The HFE deficiencies identified by FDA during review are often related to concerns that specific use errors identified in HFE studies may lead to a potential underdose or overdose of the drug constituent part. Without demonstrating that appropriate mitigations have been put in place to resolve these types of use errors, substantial design changes to the device constituent part may be required to gain product approval.”

Failure to adequately integrate the drug and device constituent parts within the overall design and development plan for the drug-device combination product is another problem, says Johns. “The bottom line is that drug and device constituent parts cannot be developed independently or in silos; cross-functional team members from both sides must communicate frequently and transparently.”

Reference
1. FDA, Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development, Draft Guidance (Feb. 2016).

—Jennifer Markarian
Enabling Technologies Advance Poorly Soluble Highly Potent APIs

Cynthia A. Challener

Excipients and new processing techniques can make a real difference in the development of highly potent therapies.

New molecular entities have continued to increase in potency over the past decade as pharmaceutical and biotechnology companies seek to improve treatment options for oncology and other chronic and rare disease areas. Approximately 70–80% of drugs in the pharmaceutical pipeline exhibit low solubility and fall into the Biopharmaceutics Classification System (BCS) Class II or IV, according to a 2015 Market Study by Kline & Co., with the majority of these compounds being Class II (poor solubility, high permeability) (1). Lonza Pharma Biotech & Nutrition reported to Pharmaceutical Technology that 20% of the current drug development pipeline is highly potent and/or requires special handling and also has solubility or permeability challenges.

While solubility and bioavailability challenges are not unique to highly potent APIs (HPAPIs) and in the small-molecule world are highly dependent upon their particular moieties and morphologies, poorly soluble HPAPIs can pose additional challenges with respect to formulation development and manufacturing. Several enabling technologies are helping drug makers and their outsourcing partners overcome these hurdles.

Multiple challenges

Any handling of HPAPIs requires care, appropriate equipment, and good practice to ensure the operator is kept safe at all times, according to Alyn McNaughton, technical director with Lonza Pharma Biotech & Nutrition. “Biopharma companies and manufacturers must be dedicated to ensuring that operators are able to do their work safely and without concern for contamination. With the technical challenges of bioavailability enhancement, additional time and dedicated experimental areas can be needed, which can make it challenging to meet development timelines,” he observes.

As one example, complex molecules designed to provide targeted activity, while minimizing side effects, also often have permeability that is limited due their larger sizes, according to McNaughton. As a consequence, the variability of absorbed dosage can be large if the product is not robustly formulated.

Even for materials where bioavailability can be readily enabled, the dosage required in the product can be incredibly low, often only a few micrograms or less, McNaughton adds. “This situation presents the secondary challenge of achieving homogeneity within the product, where an individual particle of the HPAPI may be a large portion of, or sometimes even bigger than, the specified dosage,” he says.

The particle size of APIs can strongly influence the rate of dissolution. With this approach, according to Jessica Mueller-Albers, strategic marketing director for oral drug delivery solutions at Evonik, the concentration gradient between the gut and blood vessels will be increased to facilitate drug transport and consequently absorption. However, micronized particles can be associated with increased health risks.

“The high potency of these molecules can create potential exposure concerns for workers, even at extremely small amounts. There is a need for specialized processes and expertise in the handling and containment of the drug substance, as well as intermediates resulting from particle engineering and the manufacturing of the finished drug product,” she notes.

In fact, challenges in containment can limit the technology that can be deployed for solubility enhancement, according to Adam Kujath, global senior director of manufacturing science and technology at Alcami. “Typical API approaches for solid dosage forms to improve solubility like micronization and spray drying are more difficult to outfit with appropriate containment systems. For instance, milling of solids, while not impossible to do in appropriate containment, poses a challenge since it tends to create dust in the breathing airspace for any worker. For parenteral formulations, lyophilization presents a similar challenge,” he says.

The toxicity of highly potent compounds also drives low allowable carry-
overs in the manufacturing equipment at change over. “Low solubility means cleaning reactors is inherently more challenging, and analytically may provide poor surface recoveries or impact the achievable cleaning method sensitivity. Furthermore, if they happen to be organometallic compounds, you have to worry about not only the active compound, but related organometallic and inorganic metallic species (such as mercury, arsenic, and platinum) as typical byproducts,” Kujath explains.

For contract drug-product manufacturers, the first hurdles can occur upon receipt of the HPAPI. Packaging systems can vary widely, and it is rare for the manufacturer of an HPAPI and the product manufacturer to use a common handling system, according to McNaughton. A suitable mechanism needs to be available for accessing the HPAPI in a safe and hygienic fashion.

**Effective containment**

An effective containment strategy should include clear, standardized processes for equipment startup, as well as defined cleaning procedures and robust decontamination procedures, according to Mueller-Albers. “It is integral to have operators who are well-trained in the operation of relevant equipment and procedures for the types of substances being handled,” she adds.

Any handling, introduction, and transfer of powder between processing steps must be conducted in a closed or isolated system, which requires more complex and specialized equipment, according to McNaughton. “Highly diligent processes are required to prevent operators and the surrounding environment from being exposed to dangerous airborne powders,” Mueller-Albers adds. She notes that in addition to closed systems for milling, containment systems for spray drying have also improved considerably over the past decade, which has created opportunities for the spraying of HPAPIs to form amorphous solid dispersions.

For some technologies, equipment may be specific to the individual process and require specialized handling protocols. “HPAPI product manufacturing is most straightforward for processes that have minimal steps, can be serially conducted, and do not require the material to be transferred to a completely different area,” adds McNaughton. “The resulting process commonly needs to be qualified to ensure the containment is sufficient for the product being manufactured so that any resulting operator contamination is significantly below the level at which the HPAPI could have a therapeutic effect,” he continues.

Cleaning of processes involving HPAPIs must also be conducted in a closed system and is often the time where there is the greatest risk of exposure for the operator, according to McNaughton. A key challenge for HPAPIs is the fact that cleaning must be conducted to a level at which there is no risk of contamination of subsequent products—a level at which residual HPAPIs are often difficult to detect. When detection cannot be achieved, dedicated equipment or even facilities are often required for a single product to ensure no cross-contamination with other products is possible.

Even though risks are believed to be controlled or removed, McNaughton stresses that it is important to ensure plans, systems, and training are established so that in a worst-case scenario, such as an accidental release, there is no risk of contaminating the environment and a mechanism is in place to clean the area back to a safe standard without any risk to the operators.

**Excipient options**

Excipients that are helpful in any low solubility drug are generally applicable to an HPAPI with low solubility. Solubilizers and disintegrants are two examples, according to Kujath. Excipient selection should be based on a combination of the chemical and physical properties of the HPAPI and the target product profile, according to McNaughton. “Meeting a target product profile for a poorly soluble API requires both the correct technology selection and the appropriate science-led formulation development,” he comments.

While there are no specific excipients that are suited to highly potent materials, there are certain aspects of some technologies that offer advantages if they are also the correct technology for the product, McNaughton adds. “Under certain permeability-limited situations or biological obstacles, there are specific lipidic excipients that can provide some permeability enhancement, others that inhibit efflux, and others that could avoid first pass metabolism through utilization of the lymphatic system,” he says.
The use of polymer-based excipients is widely appreciated in the formulation of poorly soluble HPAPIs, according to Mueller-Albers. They play a key role in the formation of solid solutions, stabilizing the amorphous HPAPI in the solid state to prevent recrystallization, and also helping to maintain HPAPI supersaturation in physiological media, she explains. Polymeric excipients are also used in formulations prepared via granulation using high-shear mixing or fluid-bed spraying, which can under certain conditions be applicable for poorly soluble HPAPIs.

**Enabling technologies**

The first HPAPIs were often formulated as liquids and then filled into capsules to reduce safety risks such as dust formation. Liquids, however, present challenges when solubility is an issue, according to Kujath. "While micronization and spray drying of the HPAPI can be helpful for oral solid formulations, these techniques to drive initial dissolution for liquid formulations can present stability challenges, such as crystallization of an initially dissolved amorphous HPAPI from the vehicle or ripening in a micronized dispersion," he explains. Thermocycling during terminal sterilization can also cause ripening or recrystallization or break complexes formed by solubilizers such as 2-(hydroxypropyl) beta-cyclodextrin.

As the number of HPAPIs in development has increased, however, manufacturers have aggressively examined new processing techniques suitable for oral solid-dosage forms, according to Mueller-Albers. Particle-size reduction, or particle-size design, amorphous dispersions, and lipid-based formulations are all suitable techniques for improving the bioavailability for solubility-limited HPAPI, according to McNaughton.

"Particle size reduction is likely to lead to an increase in the rate of solubility for an API and may provide some supersaturation effects, but is unlikely to result in the same level of potential increase that can be achieved by amorphous dispersions or lipid-based formulations," he says. Lipids also offer a further advantage for low-dose HPAPIs where these can be fully solubilized because the potential for poor homogeneity is eliminated and accurate dosing can be provided, even for the lowest possible dose. "Achieving such formulations may be impossible in the solid state, so a lipid/liquid approach can be enabling for the molecule to be advanced," McNaughton states.

Kujath notes, though, that while lipid-based solubilizers and the formation of nanoemulsions can be an effective way to deliver an HPAPI of low solubility, these techniques should generally be combined with the use of a low-energy means of sterilization.

If the API is not “greasy” (log P < 3), lipids are unlikely to provide the same improvements that amorphous dispersions can, according to McNaughton. In addition, processing to achieve particle-size reduction can be simpler than developing an amorphous or lipid formulation.

**Ongoing developments**

"Every day the industry is improving contamination solutions, making it easier to leverage HPAPI handling technologies that previously may have been less accessible," says Kujath. He also notes that more and more focus has been placed on not just patient safety, but on worker safety. There are always new and improved excipients being developed, new approaches, and better understanding of how to use them, agrees McNaughton. He adds that improved technologies to remove the vulnerable operator from harm include more hygienic valves, in-line testing to minimize operator interaction with potent molecules, and increased automation that completely removes the operator from the vicinity of these processes.

However, it is important, according to Kujath, to remember that the issue of low solubility is not unique to HPAPIs and can be vastly improved in the active molecule design process. For instance, he points to technologies such as antibody-drug conjugates, which are useful for targeted delivery of small-molecule HPAPIs, but also offer a means to chemically modify a pharmacologically active compound so it can be more effectively delivered if poorly soluble.

"In the small-molecule world, time spent during molecular selection for not only potency but solubility and bioavailability should be a focus in good drug design. That would reduce the need for exotic formulations to compensate. Understanding the active sites of drugs and what can be potentially modified allows for better structural designs or the creation of pro-drug analogs to increase solubility and bioavailability," he concludes.

**Reference**

Overcoming Challenges in Ophthalmic Drug Delivery Including Bioavailability and Sterility

LIVE WEBCAST: Wednesday, June 19, 2019 at 11am EDT | 8am PDT | 4pm BST | 5pm CEST

Register for this free webcast at www.pharmtech.com/pt_p/ophthalmic

EVENT OVERVIEW:
Delivery of therapeutics to the human eye is one of the most interesting — but challenging — endeavors a formulator can take on. The anatomy and chemical composition of the eye make it highly resistant to pharmaceutical penetration. Successfully circumventing these protective barriers requires intimate knowledge of ocular delivery as well as specialized development and manufacturing expertise. This webcast will explore solutions to some of today’s most challenging issues in ophthalmic drug delivery including selection of dosage form, options for increasing bioavailability, improving drug stability, properly handling highly potent APIs, overcoming patient compliance issues, and meeting the sterility critical quality attribute.

Key Learning Objectives
- Review ocular drug delivery, including dosage forms, physiological challenges, and trends
- Uncover approaches to increase bioavailability of both topical formulations and/or poorly water-soluble APIs, as well as methods to improve the stability of injectable drug products
- Discover how formulators are mitigating patient compliance issues with controlled release formulations, such as implants, long-acting injectables, and bioadhesive formulations
- Consider the various approaches to meet one of the key ophthalmic drug product critical quality attributes: sterility
- Understand the special handling requirements across a variety of ophthalmic drug products, particularly biologics and highly potent compounds such as steroids

Who Should Attend
- Formulators, researchers, scientists, biotechnology experts, innovators, drug/device engineers, and product development managers from:
  - Branded and generic pharmaceutical companies
  - Start-ups
  - Medical combination-product companies
  - Academia

For questions contact Kristen Moore at KMoore@mmhgroup.com
Poor solubility is becoming increasingly prevalent within bio/pharma drug development and is a trend that is anticipated to continue to grow as a result of the industry drive toward development of more molecularly complex chemical entities. Yet, poorly aqueous soluble compounds are not readily bioavailable for humans, and as such, these theoretically effective therapeutic molecules are severely limited in value.

“Without exploring alternative formulation techniques, actives that are highly effective in theory or during in-vitro testing may never progress through the development pipeline, and patients may never be able to benefit from them,” states Robert Lee, PhD, president of Particle Sciences. “Therefore, exploration of effective methods to improve solubility or dissolution rates of these complex molecules is vital.”

A range of techniques
There are several techniques available to help enhance solubility of drugs or to improve its dissolution rate so that a finished product with sufficient bioavailability can be developed. Approaches such as amorphous solid dispersions, complex formation, and nano-suspensions are among some of the common methods employed within the industry, Lee adds.

“It is important in development to assess a range of techniques to address the molecule-specific challenges that become apparent during pre-formulation,” he continues. “Armed with the proper knowledge and tools, formulation scientists can narrow down the potential approaches to find a strategy to provide the effective delivery of poorly soluble drugs.”

Amorphous solid dispersions. Used to overcome limited aqueous solubility and enhance oral adsorption, amorphous solid dispersions work by delivering the drug in the amorphous form. “With the API in a non-crystalline state, less energy is required for dissolution and hence absorption may be enhanced,” Lee says.

However, the potential for amorphous formulations to revert to the more stable crystalline form in storage is a major limitation of the technique. If the solid-state reverts to the crystalline form, the physical characteristics of the API are affected, which can adversely impact the solubility and dissolution rates.

“Knowledge of the solid-state characteristics of the API is required for this approach as amorphous solids may be metastable and revert to a more stable crystalline form,” confirms Lee. “Sometimes this is not observed until well into a stability program, so solid-state characteristics should be assessed in stability protocols. Proper processing and the right selection of excipients are critical for a successful amorphous formulation.”

Complex formation. In this technique, the drug and the matrix interact in an aqueous environment, forming a complex. The formed complexes augment dissolution and bioavailability of poorly soluble APIs through a low association constant, and can also enhance the stability of the drug product. In inclusion complexes, for example, stability is improved as the API is encapsulated (fully or partially) within a hydrophobic cavity of the host molecule.

“Cyclodextrins have mainly been used as complexing agents to increase the aqueous solubility of poorly soluble actives,” Lee says. “Different cyclodextrin derivatives are available, and successful development relies on the ability to select the best analogue at the right concentration.”

Yet, Lee goes on to explain that as cyclodextrin formulations are intended to be solutions, the complexes are governed by thermodynamics and have different equilibrium binding
Hot-melt extrusion (HME) is a well-known process within industry, being used since the 1930s, and more recently has found prominence in the pharma industry within the application of enhancing the bioavailability of APIs. As the industry is witnessing a surge in the number of poorly soluble drug molecules entering the development pipeline, techniques to improve solubility will inevitably continue to experience growth.

To learn more about HME, its advantages, limitations, and recent advances, Pharmaceutical Technology spoke with Michael Dennis, director of technical operations, science and technology, and Bill Huang, senior principal research scientist, formulation sciences, both from AbbVie.

**PharmTech:** Can you give a brief overview of HME and how it can aid in solubility/bioavailability enhancement?

**Dennis and Huang (AbbVie):** Historically, HME was used to convert raw materials into a homogenous solid with a particular shape. In pharmaceuticals, it also enables dissolution of APIs into a polymer to form a matrix known as an amorphous solid dispersion (ASD). ASDs achieve higher apparent solubility and faster dissolution for enhanced absorption of poorly soluble compounds (BCS Class II and IV).

In an ASD, solute molecules are dispersed molecularly randomly within the amorphous carrier. This allows for a drastic significant increase in the apparent solubility and dissolution rate achieving high bioavailability and better human pharmacokinetic/pharmacodynamic performance. A rationally formulated ASD generates drug-rich amorphous nanostructures that maximize the surface area of the compound for improved absorption when contacting the dissolution medium as the carrier dissolves.

While this technology is gaining significant traction in the pharmaceutical industry, especially in the oncology therapeutic area, it is key for anyone developing in this area to have a solid understanding of HME or to partner with someone with a strong and long tenure in understanding its nuances to ensure timely entry into the market.

**PharmTech:** What are the advantages afforded by HME over other available technologies/solutions aimed at enhancing solubility/bioavailability?

**Dennis and Huang (AbbVie):** A major advantage is that it does not use organic solvents. This significantly reduces or minimizes both environmental and safety concerns. In spray drying, an alternative method for manufacturing ASDs, for instance, organic solvents are required to dissolve the polymer and drug and then the solvents are removed during spray drying and a subsequent product drying step.

Other benefits of HME when comparing to other techniques, such as spray-drying, is that it offers shorter cycle times, a smaller footprint, and lower capital costs, which all add to its efficiency. Moreover, it is inherently a continuous unit operation, allowing fast development and scalability. HME is well placed to serve as an effective anchor for an integrated continuous manufacturing line, whether that means sequencing a continuous blender to the extruder or sizing and compressing unit operations downstream.

A well-developed ASD formulation and HME process is robust and well controlled, enabling the production of consistent product quality both intra- and inter-batch. Furthermore, HME provides an option to formulate drug products for molecules which have zero or limited solubility in organic solvents.

**PharmTech:** Are there specific limitations of HME that should be considered?

**Dennis and Huang (AbbVie):** Since HME depends on melting the polymer and drug, thermally sensitive API molecules and potentially some polymers may not be suitable. Additionally, as a result of the inherent characteristics of BCS Class II and IV API molecules, it is challenging to attain high drug loading in many cases. Further, the choice of pharmaceutical grade polymers and surfactants that are suitable for HME is still very limited.

**PharmTech:** Could you highlight the most recent advances in HME?

**Dennis and Huang (AbbVie):** Absolutely, there are numerous efforts being made by industry to advance HME. For example, the understanding of fundamental aspects of formulation and drug release has been dramatically improved in recent years, which is aiding HME product and process design and development. We have also seen industry embrace the rigorous application of physicochemical characterization tools that are helping in the understanding of the impact of physical and thermal properties of materials (constituent components as well as drug-polymer and drug-surfactant interactions) on HME processing and product characteristics. We are also seeing a surge in the use of one-dimensional and three-dimensional computational models to optimize HME processes, which is a result of computational power increases and more efficient algorithms for discrete element models and computational fluid dynamics. Through this improved understanding, it is becoming easier to develop robust formulations and processes with reduced development time and costs.

Various custom in-house modeling tools have been developed by companies, enabling scientists to select the appropriate polymers, surfactants, and drug concentration, which is supporting faster and more efficient drug development. Additionally, in recent years, there have been significant research efforts made by excipient suppliers to advance HME through the development of new polymer systems (e.g., hypromellose acetate succinate and graft polymers).

In addition to HME processes being applied to traditional solid oral drug products, they are also now being used in the formulation of biodegradable implantable products, such as poly lactic acid- and poly glycolic acid-based implants.

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The editors of Pharmaceutical Technology

constants. “Binding is an equilibrium phenomena, so large molar excesses are sometimes required for adequate complexation,” he notes. “In some cases, it may take 8 g of a cyclodextrin to encapsulate 300 mg of API. This is a relatively high dose of cyclodextrin and may be associated with real or perceived toxicity. Also, we have encountered cases where we had to optimize the encapsulation process to obtain a true solution.”

**Nano-suspensions.** Useful for oral and inhaled drug products and especially beneficial for parenterals, nano-suspensions involve the dispersion of nanometer-sized drug particles in an aqueous vehicle. In top-down methods, the API undergoes nanomilling to increase the exposed surface area, ultimately improving the rate of dissolution, which is inversely proportional to the diameter of the drug particle. “Additionally, nanomilling improves the homogeneity of a drug product and therefore content and dose uniformity,” Lee says.

Nanoparticulate suspensions, therefore, behave in a similar fashion to a molecular solution, and from a manufacturing standpoint, Lee states that the process
The appeal of nanomilling yielding a product with improved vastly differ in oral bioavailability. “Central to this knowledge base is being targeted for development to treat specific diseases over the past decade. As a result of this trend, solutions to overcome solubility and bioavailability challenges presented by these molecules are ever more vital to ensure promising molecules can be presented and delivered to market for safe and effective use by patients.”

“Molecules will continue to require ever more complex and advanced drug delivery technologies that address insoluble compounds,” notes Lee. “Not the ‘one-size-fits-all’ or ‘put it in a tablet’ approach that may have worked in the past.”

There are a variety of approaches available that can be employed by formulators to tackle the issue of solubility and increase bioavailability of poorly soluble or insoluble APIs. However, experience and expertise on how to best apply these techniques is required to give formulations the best chance of success, Lee stresses.

“Challenges in overcoming limited solubility won’t go away any time soon. But by using a rational approach to drug development, we can continue to overcome them and expand our knowledge base,” Lee summarizes. “Central to this knowledge base is being data driven and utilizing a range of techniques during formulation development alongside having the analytical and production support to take the drug products forward.”

**Conclusion**

Industry has witnessed a surge in the number of poorly soluble molecules being targeted for development to treat specific diseases over the past decade. As a result of this trend, solutions to overcome solubility and bioavailability challenges presented by these molecules are ever more vital to ensure promising molecules can be presented and delivered to market for safe and effective use by patients.

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**Formulation**

overall is efficient, reproducible, and highly scalable. “However, identifying the proper formulation composition and process are key, and a typical challenge is identifying a formulation that maintains its stability over time,” he adds. “For a formulation to be developed effectively, it requires highly experienced individuals who truly understand the process.”

So, despite the seemingly simple concept of nanoparticulate suspensions, development may not be as straightforward, with success being dependent upon the right combination of an experienced team of scientists and data interpretation to avoid formulation pitfalls. “Nanoparticulate suspensions tend to become unstable and agglomerate over time, due to high surface energy of the particles, and can also exhibit Ostwald Ripening, whereby small particles preferentially dissolve and then re-crystallize onto the larger particles,” Lee says.

Therefore, he explains that a key factor in generating a viable formulation is the optimal selection of a stabilizer. Not only must this selection process take into consideration the physiochemical and pre-formulation data on the API, but it must also factor in the primary properties of the stabilizers themselves.

“In general, there is no ‘one-size-fits-all’ approach to the selection of nanoparticulate suspension stabilizers, so often an iterative process of optimization of stabilizer selection and concentrations is necessary to achieve the final desired formulation,” Lee emphasizes. “For example, in some cases, two nanoparticulate suspensions may have essentially identical particle size distributions and physical stability but vastly differ in oral bioavailability.”

The appeal of nanomilling Out of all the approaches to formulating insoluble APIs, Lee specifies that nanomilling holds great appeal, as it is a technique that is useful for yielding a product with improved delivery and bioavailability. “Used in FDA-approved drug products since the year 2000, the nanocrystals that result from a nanomilling process can be dosed by virtually all routes of administration,” he says.

The improvement in bioavailability that is gained through nanomilling can be attributed to the fact that during the milling process, drug particles are reduced in size to below 1000 nm, typically as low as 100–200 nm, Lee explains. “The conversion to nanocrystals thereby increases the surface area-to-volume ratio of the API, which allows for greater interaction with water, which in turn increases the API dissolution rate,” he adds. “Essentially, nanomilling generates smaller particles of API, which can dissolve more readily. This creates a high concentration gradient that facilitates the transfer of the API across biological barriers including membranes (i.e., GI tract and blood brain barrier).”

Furthermore, nanomilling can be applied to nearly all insoluble APIs, Lee confirms, and the approach can be evaluated easily with only minimal quantities of API, which adds to its appeal during initial proof-of-concept study stages of development. “Nanomilling is also a particularly efficient, reproducible process that is very scalable. Once initial feasibility has been assessed and a nanomilling process is optimized, there is minimal variation in particle size from batch to batch,” he emphasizes. “This formulation approach is easy to scale to production, as commercial nanomilling equipment typically uses a recirculation process that allows batch sizes to increase without changing the process variables.”

**Growing interest in combination approach**

As an example of industry trends, Lee reveals that Particle Sciences has been witnessing a growing interest in its in-licensed technology, LyoCell, which combines a lipid-based approach with nanoparticles. “The technology uses a reverse cubic-phase matrix, which assures the hydrophobic and hydrophilic domains in these nanoparticles are never more than a few nanometers apart, potentially leading to unique solubilization properties,” he explains. “Alternative lipid-based approaches such as emulsions (hydrophobic core) or liposomes (hydrophilic core) offer a micro environment that is either hydrophobic or hydrophilic but not both. The LyoCell micro environment offers both, and is therefore, better suited for typical drug-like molecules that are often amphiphilic (i.e., containing both a non-polar hydrophobic region and a polar hydrophilic region).”

The technology is intended for a range of applications, suitable for a wide variety of dosage forms, and employs generally recognized as safe (GRAS) ingredients.

**Conclusion**

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**PT**
A connected MDI may encourage compliance and aid proper technique.

Can “smart” drug-delivery devices improve patient compliance? Innovators at 3M think so. Improving adherence and reducing use errors in noncompliant patients have been associated with improved health outcomes, and smart inhalers have the potential to help accomplish this objective, says Stewart Griffiths, a product commercialization manager for 3M Drug Delivery Systems Division. “As a society, we’re growing more accustomed to getting the information we want faster than ever before and in a way that is tailored to our individual preferences,” he notes. “Everyday is personalized and on demand. We are starting to see this becoming true with regard to how drugs are delivered to patients and the instant feedback they expect.” Pharmaceutical Technology spoke with Griffiths about the company’s 3M Intelligent Control Inhaler, which is currently in development, and about some of the manufacturing and regulatory considerations for connected combination drug-device products.

**Patient-centric design**

**PharmTech:** Can you briefly describe how the 3M Intelligent Control Inhaler functions?

**Griffiths (3M):** Most pressurized metered dose inhalers (pMDIs) on the market require you to coordinate your inspiratory flow when you press down on the canister to release the medicine. If you breathe in and your lungs are nearly full by the time you press, you’ve pressed too late. Conversely, you may press too early in the inspiratory cycle. When you mistime it, less medicine than intended is absorbed.

The 3M Intelligent Control Inhaler was designed such that it could utilize the familiar MDI dosage form and add value by aiding patient coordination. It uses breath actuation to help correct the coordination problem, so you just breathe in and the drug is automatically delivered when you are inhaling and before your lungs are full. In addition, the display can visually prompt patients on how to use it correctly. This inhaler has been designed to be reusable. The main electronics component is reusable with up to 12 monthly refills of the medicine.

**PharmTech:** What are some of the benefits of connecting inhalers to a smart device?

**Griffiths (3M):** It stands to reason that you can get better patient engagement through ease of use, which can lead to improved compliance. My interpretation of compliance is twofold. The first element is adherence. Is a patient taking his/her medicine at the right time, in the right amount, as prescribed? On a daily basis? Morning and evening? The correct number of puffs each time, as necessary? Are they doing that routinely?

The second element is technique. With inhalation therapy, the delivery of the medicine can be greatly affected by how a patient uses a device. We see many delivery issues with press-and-breathe inhalers, soft mist inhalers, and dry powder inhalers. With some dry powder inhalers, a patient needs to use a lot of inspiratory force to deliver the drug, which is difficult for some patients with respiratory diseases to attain.

Technology can help in both areas. An inhaler that is connected with a smart device can send reminders to a patient to help with adherence, for example. It also has the potential to help improve technique by providing feedback to a patient. The 3M Intelligent Control Inhaler was designed with the potential to do this. We wanted to have the ability to tell patients when they’re not breathing in for long enough or when they’ve not shaken the medicine if it needs to be shaken. Technology gives us the ability to coach and guide patients in the real world, without having to be in a doctor’s office.

**PharmTech:** How do you incorporate human factors engineering into a device design?

**Griffiths (3M):** From my perspective, it is important to get the device into the hands of patients as early as possible—for example, through formative human factors studies in the early prototype stage. These studies allow the scientist in the lab
to use input from real patients to design new inhalers that are easy to use, fit comfortably in hand, and are easy to actuate, for example. Only when you put it into the hands of patients will you discover that it may be fundamentally flawed. Those formative human factors studies act as inputs that can inform the design of the device. When patients can easily operate a device, it means the patient receives the correct dose and is more likely to comply with the therapy.

One of the key outputs of a human factors program is the instructions for how to use the device. The findings will drive what goes into those instructions. They will also inform how the packaging is designed, to ensure that it is easy for patients to open.

**Regulatory considerations**

**PharmTech:** What are the regulatory and data security concerns with connected devices and how are they being addressed?

**Griffiths (3M):** Protecting patient privacy must be a top priority. There are tremendous opportunities ahead for collecting, sharing, and analyzing data generated by digital delivery devices; however, we need to instill trust in patients from the very beginning. To do that, we need to make sure patients understand how and why we’re using their data, and we need to clearly demonstrate how they will benefit from the use of their data. Today, it is critically important to determine the data strategy before going into design and development. 3M has addressed this by making security part of the up-front development process.

Finally, regulations around drugs and devices are now becoming intertwined with electronics and software. 3M’s goal is to be ahead of the curve and follow the regulations as they evolve. The speed of electronics and software evolution is at a much faster pace than traditional pharmaceuticals by nature. The industry needs to evolve to incorporate electronics but continue in a safe way.

**PharmTech:** What are some of the manufacturing challenges for incorporating electronics into inhalers? Are there special regulatory/quality testing considerations for connected devices?

**Griffiths (3M):** From a manufacturing point of view, the arrival of connected devices requires a shift from purely plastic components to the incorporation of electronic components. This not only requires updates to the manufacturing lines themselves, but to the testing facilities. If historically you’ve worked only with plastic materials, tests are purely physical in nature. Electronics module testing is very different. For instance, if your connected inhaler utilizes Bluetooth technology, electromagnetic compatibility testing is required to prevent the device from interfering with other connected devices. Regulatory standards also change, once a device is categorized as connected.

Finally, with technology constantly changing, the use of electronics allows for rapid improvements and the ability to address real patient issues. For instance, improved battery technology can allow a device to be used for a longer period of time. At the same time, it is important to keep in mind that the pace of the pharmaceutical industry is very different than the pace of the technology industry. This can create major challenges on everythine from the design to the manufacture of a device.

**PharmTech:** What is your technology doing to keep up with these changes?

**Hovione:** We believe that packaging plays a role in achieving compliance. We have made great strides in the development of blister-based inhalers, like our aerosol-DPI-based technology, which has been the gold standard for years. We are also working on developing connected devices that can monitor patient compliance and provide real-time feedback to improve medication adherence.

**Inhalation Drug Manufacturing**

Hovione Technology, a Hovione Ventures company, announced in an April 15, 2019 press release that it has secured global rights to develop and commercialize a new, affordable, multi-use blister-based dry powder inhaler (DPI) patented by inventor Dr. Klaus-Dieter Beller, which will be marketed as the Papillon DPI (1). The blister-based inhaler is suitable for both chronic and acute treatments and can accommodate a single- or double-blister configuration. The patient loads a blister to take the daily dose and reuses the inhaler for a defined period of time, typically 30 or 60 days.

The simplicity of the device, which is made from a single part, significantly reduces development cost and risk compared to more complex devices, explains Hovione Technology’s CEO Peter Villax and João Ventura, director of Technology Development and Licensing. “Because it is manufactured from a single mold, manufacturing and depreciation costs are much lower,” they add.

Villax and Ventura say that simpler DPI designs, which are less costly to manufacture, fulfill the need for readily accessible and affordable treatments, particularly in less developed markets. “Innovators have traditionally used device complexity to increase development and cost barriers for generic competition. [In addition,] smart and connected devices may have a role in the medium-term to further improve treatment effectiveness and adherence, especially in developed markets,” notes Ventura. “But inhaler devices do not fundamentally need to be complex; inhaled drugs can be delivered as effectively from devices made of very few parts and assembly steps.” Ventura says that making simpler inhaler devices is also a “greener” solution that consumes less resources.

Hovione Technology Develops Blister-Based Inhaler

In addition to being simple to manufacture, devices need to be simple for patients to use correctly. “Inhalers need to work in the hands of the patient. No matter how brilliant our inventions are, at the end of the day they need to bring benefit and value to the patients,” says Villax. He explains that human factors engineering is central for new DPI developments. This systematic design process can capture preferences towards design attributes that support patient engagement with the device.

Creating a simple DPI is not a simple task. It is a difficult “marriage between device physics and formulation properties,” says Villax. “An inhaled combination [drug] is a complex product, because you have to consider not just the drug, but also how they interact with each other. For example: a powder inhaler turns an inspiratory effort into a force that disperses and aerosolizes a powder and entrains the particles into the lung. How efficiently this dispersion and entrainment occur is a key feature of the inhaler, but it depends just as much on the particles themselves and on how well they fly.”

Hovione Technology’s co-promotional agreement with API manufacturer Hovione allows the company to integrate DPI device development with inhalation API formulation development and manufacturing. According to Hovione Technology, Papillon is available for feasibility studies and integrated development with formulation by pharmaceutical partners.

**Reference**


—Jennifer Markanian
Batch or Continuous? Ask the Right Questions During Scale Up

Agnes Shanley

Continuous manufacturing may offer huge opportunities, but it will not be right for every facility or product.

On May 6, 2019, at St. John’s University in New York City, the 11th annual Charles Jarowski Symposium in Industrial Pharmacy examined the challenges and opportunities posed by continuous pharmaceutical manufacturing. A number of commercial products are already being made continuously, and more than 20 products that are now awaiting FDA approval use continuous manufacturing, said Atul Dubey, director of pharmaceutical continuous manufacturing at the United States Pharmacopeia (USP), who spoke on the program.

A crucial question is what the incentives will be for generic pharmaceutical manufacturers, which supply most of the prescriptions written in the United States, to invest in the technology and knowhow that continuous manufacturing requires. “How can we make continuous manufacturing easier for late adopters? In the end, we need to promote the quality of medicines, however they are made,” said Dubey. “We will also need to be able to produce drugs that were approved as continuously manufactured products so that they can be made via batch manufacturing,” he said, “since the reality is that not all manufacturers will embrace continuous manufacturing.”

At the program, experts from Merck and Takeda discussed continuous manufacturing pilot development programs underway at their companies, university professors summarized research findings, and Bayan Takizawa, co-founder and chief business officer at Continuus Pharmaceuticals highlighted pilots and projects underway to help advance end-to-end continuous manufacturing, from API to finished product.

QbD becomes more dynamic

A number of speakers suggested that the concept of pharmaceutical quality by design (QbD) is becoming much more dynamic than what was outlined in the first FDA guidance on that topic. As pharmaceutical manufacturers have become more comfortable with more advanced process control, the emphasis is moving from the design space to greater use of feedback control. The idea, according to Zoltan Nagy, a professor at Purdue University’s School of Engineering, is “to make critical quality attributes tunable so that the system can find the conditions at which it needs to operate in order to ensure product quality.” Ajaz Hussain, director of the National Institute for Pharmaceutical Technology and Education (NIPTE), spoke of the need for reproducibility and repeatability, and to move from “one size fits all” attributes to multivariate personalization. “Twenty-first century quality and cures demand continual improvement and confidence, and that will require dynamic feedforward and feedback control,” he said. For a full report on the symposium, visit PharmTech.com.

Scale-up considerations

Focusing on scale-up issues was Michael Rooney, director of process engineering at Genesis Engineers, who considered some of the challenges that existing manufacturing operations face when considering the implementation of a continuous manufacturing approach to scale up oral solid dosage (OSD) forms or replace a batch process with continuous. As he explained, one cannot simply inject continuous manufacturing into a batch facility, especially because legacy facilities tend to be single or two stories, and floor-to-floor distances do not help vertically integrate continuous. Rooney used two different case studies to illustrate the challenges of justifying the cost to convert to continuous. One involved the
expansion of a commercial drug using a dry granulation process in an established facility, the other, expansion of a high volume over-the-counter (OTC) product that did not involve API. In this case, he said, reducing labor costs was the primary goal.

“People tend to emphasize the potential for continuous manufacturing to reduce [costs] ... but it may require increased investment in PAT, process development, data handling and storage, and recall strategies.”

— Michael Rooney, Genesis Engineers

Conflicting material flows
In both cases, he said, using the continuous manufacturing scenario, the flows of people and raw material conflicted. “What began as a capacity question ended up as a question of return on investment,” he said. For one thing, with the branded drug company, it was found that the building, which was only 25 feet high, would need to be 60 feet high to accommodate continuous manufacturing. In addition, the shift from batch manufacturing would involve higher operating costs due to highly skilled technicians to attend to the PAT technology. The company, which had been trying to justify moving to continuous manufacturing on the back of one major product, is now working on building a continuous platform. “If you develop a platform for groups of product types, rather than try to replace existing batch capacity with continuous, it doesn’t have to run 100%. You can build a platform and a portfolio over time,” Rooney said.

In the second case, with the OTC product, second-level infrastructure costs hurt financials and there was no subject matter expert on site to develop the process analytical technology (PAT) required for continuous, Rooney said. In this facility’s case, moving to continuous had no real impact on manufacturing to reduce the cost of goods sold (COGS), but it may require increased investment in PAT, process development, data handling, and storage and recall strategies,” he said.

In the end, companies must determine what will be more cost effective: reducing operator labor and facility costs or reducing time to market and starting to recoup product revenue sooner. For most companies, the transition to continuous manufacturing will be driven by product development scientists and engineers sooner than it will by the operations group, Rooney said. In addition, savings may often be more pronounced in Phase II and Phase III projects, rather than commercial production. In an interview after the Conference, Rooney shared some insights into continuous pharmaceutical scale up with Pharmaceutical Technology.

Labor or time-to-market?
PharmTech: Are there some basic misunderstandings in the industry today about continuous manufacturing and how easy it is to scale up?

Rooney: I’m a real proponent of continuous manufacturing, but it’s not perfect for everything.

PharmTech: What would make a process an ideal candidate for continuous manufacturing?

Rooney: Generally, continuous will be most practical for processes that involve direct compression or dry granulation. With direct compression, one is mixing components with minimal manipulating. In dry granulation, material is densified with a roller compactor, milled, blended, and compressed with a tablet press. Tablet press equipment has long been based on a continuous process anyway. In addition, the percentage of active shouldn’t be too low if a continuous approach is to work well, or at least be easy to implement. In some new oncology drugs, the API is so potent that drugs may only contain about 1–5% active ingredient. Using continuous manufacturing for these products can be very challenging, even though it is possible, because of the need to guarantee plus or minus 10% of label claims.

In addition, these formulas typically use a large number of other functional components (e.g., pH neutralizers and disintegrants). Sometimes up to 14 different components may be required, all in differing quantities. The best candidates for scale up using continuous manufacturing are products that involve dry granulation and direct compression, products where API percentages aren’t too low, and where there aren’t too many diverse excipients in the formulation.

Making the case to management
PharmTech: Are there considerations that people may forget when they propose continuous manufacturing projects to corporate managers?

Rooney: On the manufacturing side, the idea to use continuous often comes from managers who see continuous as a way to reduce labor and equipment footprint. Continuous will save both, but there are other factors to consider. In batch OSD plants, when you move material around you promote segregation or unblending. Continuous minimizes this movement, so managers may think it will help reduce segregation and even reduce the need to wash bins as frequently. But this is only part of the challenge. Based on data gath-
ered during continuous manufacturing, facilities can use real-time release, eliminate testing and product quarantine and release to distribution. There is no worry about batch size, because batches are defined by time, with process validation documents establishing the maximum operating window. The challenge comes with using PAT. One has to characterize that product that is going through the process. Current PAT technology is capable of generating data in a matter of seconds and accumulating data very quickly, that has to be controlled, stored, and potentially retrieved at a later date. The equipment cannot run without the PAT working, but then how does the PAT system know how to work?

PAT learns the comparator or monographs, which reflects thousands of hours of development. PAT takes a snapshot of what is moving past the analyzers, and compares the value to that from a monograph. But what if some peaks have shifted? There can be different sources of variability, which require multivariate analysis. This is not strictly an equipment decision.

Consider facility layout

**PharmTech:** Do people underestimate the challenges posed by facility layout?

**Rooney:** With continuous, one attempts to solve a lot of problems about particulate separation by coupling everything (e.g., placing feeders near blenders, and blenders near mills). Another challenge is the conversion of a formulation from batch to continuous considering the number of raw materials to be included in the process. You may only be able to blend three raw material ingredients in one blender, so if you are working with many ingredients, you may have to do a pre-blend that will then go into another blender, then add more material and send it to yet another blender.

You also have to select where you want to place your PAT system. In short, you are stacking operations vertically with many systems capable of failure or inaccuracies. Also consider that all these feeders must be fed via bulk containers. One of the big advantages of continuous is that it allows a facility to bring raw material containers straight into your plant and not stop to dispense individual batch materials. However, this is the opposite of what people in batch plants have been doing for the past 20 years.

In most batch facilities today, the dispensary is the dividing line between current good manufacturing practices (cGMP) and non-cGMP operations. Bulk corrugated containers can introduce contaminants into a facility. In general, the flows that are required for continuous manufacturing are counterintuitive to what people generally have, and there is a very different space classification for each.

More CDMOs working in continuous

**PharmTech:** What might convince more generic pharmaceutical manufacturers to invest in continuous technology?

**Rooney:** I expect to see faster integration of continuous manufacturing in the OTC market, particularly for supplements. These lines run at much higher speeds and labor is a big component of their cost of goods. Continuous manufacturing allows OTC manufacturers to reduce operating costs.

For generic pharmaceuticals, the issues are different. Branded companies are not all going to share their development databases, monographs, and approaches to PAT, so generics manufacturers would have to invest in the same development that branded companies have to do. I expect to see more contract development and manufacturing organizations (CDMOs) investing in continuous manufacturing. Generic pharmaceutical manufacturers would be more likely to work with these CDMOs, to avoid having to invest in continuous manufacturing technology and expertise themselves.
Data integrity ensures that information stored during pharmaceutical manufacturing is reliable and trustworthy. Electronic records (e-records) pose special data integrity challenges. Links between electronic data, raw data (i.e., the first capture of information, whether recorded on paper or electronically [1]), metadata, and records must not be compromised or broken if the data and their relationships with other data are to be valid.

Preserving the integrity of the raw electronic data generated by manufacturing and quality operations is crucial because these data provide the only evidence that these departments are being run and managed correctly and in a way that complies with regulations. It is the foundation for continuous process verification (CPV) and process validation. Technological controls must be in place to ensure the integrity of these data. This article discusses these controls and how they should be implemented for identification, storage, protection, retrieval, retention time, and disposition of current good manufacturing practice (cGMP) records (2).

Data lifecycle
The data lifecycle (Figure 1) helps to map and explain the controls that are necessary to manage data, raw data, metadata, and records (3) properly. Data access control is crucial, for example, and any changes to an e-data point can only be made by someone who has been authorized to make those changes. Failure to address even one element of the data life cycle will weaken the overall effectiveness of controls implemented for the computer system and for e-data integrity.

During the data capture stage, data are collected and related actions are performed. Then, during transformation, the data are scaled and converted, and then built-in checks (summarized in European Union [EU] Annex 11-11 [4]) are performed to verify that all the data are correct after the transformation.

Because the data transferred during this stage move between process equipment and the computer, the interface between the two should be validated and checked periodically to ensure accuracy. The accuracy and reliability of the raw data depend not only on properly calibrated and maintained instruments and equipment, but also on the integrity of the raw data that have been recorded. When instruments and equipment cannot ensure secure data access and administration of electronic data files, collected
LabVantage Pharma is the only pre-validated, pre-configured, 100% web-based informatics platform designed specifically for pharmaceutical QA/QC manufacturing. It is also the first LIMS to enable compliance with global draft guidance for data integrity.

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In these types of operations, data that have been loaded from field sensors contain a measurable attribute of a physical entity, process, or event (5). The loaded data are recorded, becoming raw data, which are considered “original” or “source captured” (6). When multiple raw data are generated to satisfy a cGMP requirement, such raw data become a cGMP record (7). Examples of raw data in a typical manufacturing environment include:

- Analog readings (e.g., of temperature, pressure, flow rates, levels, weights, central processing unit [CPU] temperatures, mixer speeds, or fan speeds)
- Digital readings (e.g., of valves, limit switches, motors on/off, and discrete level sensors)
- Product information (e.g., IDs for product, batch, material, or raw material lot)
- Quality info (e.g., process and product limits, custom limits)
- Alarm info (e.g., out-of limits or return-to-normal signals)

The raw data hold the content of the e-record that will reproduce the full cGMP automated activities (8). Properly recorded and managed raw data are the foundation that is required to demonstrate the product identity, strength, purity, and safety. The e-records associated with raw data demonstrate that the manufacturer’s processes meet the requirements of cGMP, including those for process sequencing and instructions (9).

Accurate management of data during entry or collection, storage, transmission, and processing (10,11) provides controls required for the processing and retention of loaded data, raw data, and e-records. The integrity of manufacturing raw data is a basic prerequisite to CPV, an essential part of FDA’s process validation requirements. CPV is designed to provide continual assurance that the process remains in a state of control during commercial manufacturing. The collection of information about the performance of the process will allow detection of undesired process variability so that the process remains in control.

Identification of cGMP records

Identification to the cGMP records (12) and associated controls are crucial to the success of any pharmaceutical manufacturing operation. The characterization of these cGMP records usually starts with a primary design document such as a process and instrumentation drawing (P&ID). A process flow diagram (PFD) or some other form of schematic may also be used.

Table I depicts the critical process parameters for a solid dosage form manufacturing process. Process equipment incorporates instrumentation designed to control the process and acquire data about each critical process parameter.

The primary goal for controllers is that they work accurately in the intended process. The controllers are dynamically verified during the qualification of the automated cell controller. The cell controllers are typical Level 0 in the ANSI/ISA-95 and essential to ensure proper functioning of the process and product quality. The input/output (I/O) list refers to the information that comes into and goes out of the manufacturing system.

In Table I, for example, the air temperature, air volume dew point, and product temperature are the I/Os associated with a fluid bed dryer (13). Field instruments provide measurements of these values from field instruments via terminating wires in the digital system I/O processing section. After transformation, the data are transmitted to the SCADA system over the communications link.

The first step in documenting the I/O requirements is to compile a list of all the applicable points that are referenced on the

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**Figure 1: Data lifecycle.**

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<tr>
<th>Processable Data</th>
<th>Archiving</th>
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<td>Work in progress</td>
<td>Commit to collect</td>
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<tr>
<td>Capture and transformation</td>
<td>Commit to use</td>
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<tr>
<td>Data change management</td>
<td>Commit to archive</td>
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<tr>
<td>Active phase access and use</td>
<td>Deletion of records</td>
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<td>Inactive phase</td>
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<td>Discard</td>
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P&ID. This is necessary so that the specific signal and termination data can be associated with each point or each instrument. Alarms and reporting requirements must also be considered.

Storage of records

Raw data are original records generated by means of computer systems and become the contents of an e-record. E-records storage devices record, store, or retrieve e-records from any medium, including the medium itself. This is considered a short retention environment. Design specifications or similar documents must describe the file structure(s) in which the e-records are to be stored, as well as the capacity requirements of the storage, and how the security scheme is implemented. The file structure and security are verified/tested during the qualification.

After the data are recorded and retained by computer storage (e.g., historian/SCADA storage), the physical and logical controls to the e-records must be in place. These controls include physical protections, stamped audit trail, data management, archival and retrieval of records. Alarms and the associated actions to the alarms are managed by the programmable logic controller (PLC). The associated alarm records are saved in the corresponding repository system at the storage device level. Physical protection is important because environmental effects can cause media to deteriorate. Copying information without changing it offers a short-term solution, ensuring that information is stored on newer media before the old media deteriorate to the point where the information can no longer be retrieved.

To ensure data integrity during storage, any changes that have been made to an e-record must be recorded, including the previous entry, who made the change, and when the change was made (14). To reduce the risk of losing the e-records in storage and to guarantee that they will be ready for use, data must periodically be backed up. Backup data must be stored separately from the primary storage location, and at a frequency based on an analysis of risk to CGMP e-records and the capacity of the storage device. The efficacy of the backup and restore processes must be verified as part of the qualification process. In addition, the capacity level of the storage must be monitored. As in archived e-records, the e-records in storage need to be verified periodically for accessibility, readability, and integrity. If changes are implemented to the computer infrastructure and/or application, then it is required to ensure and test the ability to retrieve e-records.

One critical element to consider is legal holds to the e-records, which may exist when the manufacturing company or contract manufacturer is involved in litigation. These records cannot be destroyed, even if the data retention period has expired. The regu-

<table>
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<th>Table I. Critical process parameters for solid dosage form manufacturing.</th>
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FOR PERSONAL, NON-COMMERCIAL USE
lated entity is under a legal obligation to retain all relevant, and a legal holds record system or other mechanism must be implemented to identify e-records that would be affected by a legal hold.

In optimizing physical location requirements for the e-data, web and database servers should ideally be separated. Database servers should be isolated from a website's demilitarized zone (DMZ), based on security standards. A DMZ is a physical or logical subnetwork that contains and exposes an organization’s external-facing services to a larger and untrusted network, usually the Internet. The purpose of a DMZ is to add an additional layer of security to an organization’s local area network (LAN); an external network node only has direct access to equipment in the DMZ, rather than any other part of the network (15).

These servers can locate them on a physically separate network segment from the web and other Internet-accessible servers that support the business. Preferably, one should partition the database server off from the web servers by a dedicated firewall. This firewall should only allow database traffic between the web server and database server. The firewall should also deny and log all traffic from any other location, or other types of traffic from the web server. Regulators, and particularly FDA, expect that data written in the storage device be saved at the time they are generated (16). As appropriate, it is the expectations of the regulatory authorities that the data written in the storage device must be saved at the time the data are generated (17).

Protection of data and records
The protection of transient data, raw data, and e-records cover data in storage, during processing, and while in transit (18–20). The protection of transient data, raw data, and e-records may be set in two environments: transient data before reaching the historian/SCADA and raw data, as shown in Figure 2.

**Transient data.** At the PLC level, the analog data are extracted from the PLC memory, transformed (i.e., digitized, validated, normalized, and scaled) and sent to the SCADA. The data collected directly from manufacturing equipment and control signals between equipment and a data server (e.g., SCADA) may be regarded as transient and cannot be edited by reasonable means or reprocessed by the human user. Similar to the controls associated with e-records in transit, the data integrity controls for transient data are:

- **Qualification of the infrastructure.** The outcome of this qualification provides documentary evidence that accounts for the correct implementation of integrated hardware and associated devices (21).
- **Built-in checks for the correct I/Os.** These built-in checks are, at first, validated. During the operational stage, the built-in checks must be periodically verified (as required by FDA 21 US Code of Federal Regulations (CFR) Part 211.68(b) and EU Annex 11-5) (22 and 23).

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**Figure 2: Data integrity and e-records in process automation. SCADA is supervisory control and data acquisition; I/O is input/output.**

**Data Integrity and E-records (ER) in Process Automation**

Data collected directly from equipment and control signals between computers and equipment should be checked by verification circuits/software to confirm accuracy and reliability.

TGA, Code of GMPs, 2013.
• **Accuracy checks.** Usually performed at the supervisory system level, accuracy checks are required for critical data that have been entered manually by authorized personnel. These critical data require input verification to prevent incorrect data entries.

After the data are recorded and retained, physical and logical controls to the e-records must be implemented and executed. These controls include security, access authorization, backups, periodic reviews, stamped audit trails, built-in checks (required by FDA Compliance Policy Guide CPG Section 425.400), and other relevant data-management controls. The PLC manages alarms and associated actions, which are saved at the storage device level. Controls are required if the e-records and associated raw data must be transferred from the original processing environment. After concluding the migration process, verification must be performed to ensure that the information in the original e-records has not been altered. This verified copy becomes a true or certified copy.

**Retrieval of records**

Access to e-records should be ensured throughout the retention period (as required by EU Annex 11-7.1). The access to these records must be controlled to ensure the integrity of the e-records in storage. The controls associated with e-records in storage allow those individuals who depend on the e-records to correctly fulfill their job functions.

During the Active Phase, manufacturing e-records will typically be held in the environment in which the records were initially created. In this environment, the e-records are visible to the tools that created them. Any features designed to allow them to be changed or deleted must ensure audit trails that record the reason for change or deletion, as well as other information as required by the applicable regulation.

Periodic (or continuous) reviews must be performed after the initial validation (as required by EU Annex 11-11) of the processing environment. These reviews check stored, backup, and archived e-records for accessibility, readability, and accuracy. They also verify the output of the backup and the accuracy of the overall audit trail, verifying the accuracy and reliability of the e-records transferred (WHO 3.2). In addition, processes for reading and managing e-records must ensure their data integrity. The infrastructure between the records in storage and the processing environment must be a controlled environment and must be qualified and checked for accuracy.

**Data retention time**

The EU cGMPs establish that raw data supporting information in the marketing authorization (24), such as validation or stability data, should be retained while the authorization remains in force. In some cases, periods up to 30 years’ worth of raw data must be retained. It may be considered acceptable to retire certain documentation when the data have been superseded by a full set of new data. In such cases, justification should be documented and should take into account the requirements for retention of batch documentation. The accompanying raw data should be retained for a period at least as long as the records for all batches whose release has been supported on the basis of that validation exercise.

For a medicinal product, the batch documentation must be retained for at least one year after the expiry date of the batches to which it relates, or at least five years after the certification referred to in Article 51(3) of Directive 2001/83/EC, whichever is the longer period. At least two years of data must be retrievable in a timely manner for the purposes of regulatory inspection.

Applicable FDA regulations, 21 CFR 211.180(a), call for data that are part of the drug product production and control records to be retained for at least one year after the expiration date of the batch or, in the case of certain over-the-counter (OTC) drug products lacking expiration dating because they meet the criteria for exemption under 21 CFR 211.137, for three years after distribution of the batch. As the results of the traceability requirements, the raw data will be retained as specified in 21 CFR 211.180(a).

When computer systems are used instead of written documents, the manufacturer shall first validate the systems by showing that the e-records will be appropriately stored during the anticipated period of storage. E-records stored by those systems shall be made readily available in a legible form and provided upon the regulators’ request. The electronically stored e-records shall be backed up and protected against loss or damage, and audit trails shall be maintained.

**Disposition of records**

If active records are transferred to another environment, validation should include checks that data have not been altered in value and/or meaning during this migration process, as required by EU Annex 11-4.8.

E-records that are placed in retention environments, other than the environments that were used for their original creation, should preserve the integrity of the raw data, associated e-record, and protection mechanisms used to prevent informational loss and/or corruption. Should records require modifications in retention environments, a clear audit trail of change or replacement history, including record removal, should be maintained.

Once e-records have been placed in the retention environments, they should never be directly modified. If technical limitations require the electronic record to be modified in the retention environment, the change must have traceability to the same change in the processing environment. The inactive phase starts with records archival. These records need to be kept to meet retention schedule requirements and traceability. These records usually maintain read/view attributes. Finally, during the deletion phase, the e-records are discarded. This is a phase of short duration and includes metadata and audit trails.

**References**

More structured assessments

The modern drug assessment system under KASA will build on algorithms of risk and support computer-aided analysis for a structured assessment of an application. The process begins with an objective evaluation of risk that considers key critical quality attributes, enabling OPQ staff to focus on more risky products. The analysis considers the severity of possible harms and the detectability of future failures to be able to compare risks across products and determine if attributes are within or outside acceptable ranges. With such information, CDER still may approve a risky product, but with a recognition of the need for greater oversight to control for possible future problems.

In making the case for KASA at the PQRI meeting, OLDP Director Susan Rosencrance observed that applications for new drugs and generics composed of unstructured text can be a hindrance to an efficient agency assessment of product quality. Too often, she said, the important information on how an applicant controls risk “is lost in hundreds of pages of text.” This may encourage a reviewer’s quality assessment to be more subjective, leading to inconsistent decisions by the agency.

Drug applications that present information in prose require reviewers to do “a lot of hunting and pecking” to pull out key data, added Mary Ann Slack, director of CDER’s Office of Strategic Programs. To move forward, FDA plans to develop and test electronic data standards for submitting product quality and chemistry, manufacturing, and controls (CMC) data to the agency, Slack explained. This will be described in draft guidance slated for publication by March 2020 to further explain how future applications should present data files that can be entered into FDA’s drug data system to check ranges and areas to review more closely.

KASA is part of broader CDER efforts to modernize its drug regulatory program. This includes reorganizing the Office of New Drugs, developing new IT platforms and applications, establishing quality metrics, and building the emerging technology program to promote new drug design and manufacturing strategies. More consistent and objective regulatory assessments under KASA fits these broader goals by helping FDA achieve more first-cycle approvals for manufacturers and more affordable and accessible medicines for patients.

References

EVENT OVERVIEW:
Historically, distillation has been the most common technology used to produce Water for Injection (WFI). Changes in the European Pharmacopeia no longer require the use of distillation systems to produce WFI. In this webcast, learn about the impact of this regulatory change on water system design and how reverse osmosis and ultrafiltration can be used to produce WFI with significant lifecycle cost advantages.

Subjects that will be covered include:
- WFI regulatory requirements
- How to design a WFI system with non-distillation technologies
- How to convert an existing system to WFI production
- What is required to qualify a membrane-based WFI production system

Who Should Attend
- Project Engineers, Plant Engineers, Facilities Engineers, Quality Control, Regulatory Affairs, and A&E Firms

Register for this free webcast at www.pharmtech.com/pt_p/membrane

Presenters
Gary V. Zoccolante
Technical Director
Plymouth Rock Water Consultants

Rich Jarrett
Director of Pharmaceutical Marketing
Evoqua Water Technologies

Moderator
Rita Peters
Editorial Director
Pharmaceutical Technology

For questions contact Martha Devia at MDevia@mmhgroup.com
Many of the highest-grossing protein therapeutics, including monoclonal antibodies (mAbs), Fc-fusion proteins (etanercept [Enbrel, Amgen/Pfizer] and aflibercept [Eylea, Bayer/Regeneron]), interferon gamma (IFN-α), erythropoietin (EPO), and tissue plasminogen activator (tPA) contain complex carbohydrates (glycans) covalently bound to their peptide backbone (1). In turn, the presence and relative abundance of different glycan motifs (e.g., α-1,3 galactose, core fucosylation, and sialylation) are well-known to influence the safety, serum-half life (pharmacokinetics), and the therapeutic mechanisms (pharmacodynamics) of the aforementioned biopharmaceuticals (2).

Glycosylation is also widely acknowledged as a major source of therapeutic protein heterogeneity (3), which is highlighted by work that found considerable glycosylation variation among different commercial lots of the same biopharmaceutical product (4). Biopharmaceutical glycosylation variability is determined by manufacturing bioprocess conditions (1). Large-scale mammalian cell culture is used for the manufacture of all therapeutic glycoproteins (TGPs), with Chinese hamster ovary (CHO) and murine myeloma (NS0 and Sp2/0) cell lines being the most-commonly used production platforms (5).

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In the context of biopharmaceutical quality assurance, 21 mathematical models for protein glycosylation have been developed over the past decade. Although the strategies to mathematically describe the glycosylation process have been diverse, all models have demonstrated potential toward addressing one or more quality assurance (QA) issues associated with TGP manufacture. This review focuses on how different modeling strategies can be leveraged to aid in product QA across the different stages of biopharmaceutical product development and manufacture. Technical details on glycosylation models have been outlined elsewhere (6).

Glycosylation impacts the safety and efficacy of protein therapeutics

The following individual glycosylation motifs that are known to influence the safety, pharmacokinetics, and pharmacodynamics of TGPs are presented in Figure 1:

- Presence of high-mannose glycans, in particular, the five-mannose glycan (Man5), reduces the serum half-life of antibodies (7). Man5 may also enhance antibody-dependent cellular cytotoxicity (ADCC) (8), a mechanism that improves the oncolytic activity of mAbs.
- Tandem α-1,3 galactose is a non-human glycosylation motif that is produced by murine cell lines, such as NS0 and Sp2/0 (9) and has also been observed in CHO cells (10). Presence of α-1,3 galactose residues has been reported to cause fatal anaphylaxis in patients treated with Cetuximab (Erbitux, Bristol-Myers Squibb/Merck) (9,11). These cases occurred in patients who were allergic to α-galactose, a condition likely caused by exposure to tick bites (9,11). To avoid these reactions, patients are now screened for α-galactose allergy prior to treatment with Cetuximab (9,11).
- The absence of core fucose has been reported to enhance mAb ADCC activity up to 50-fold in in-vitro studies (12). Cell engineering stra-
strategies to eliminate core fucosylation have resulted in two commercially-available glycoengineered mAb products, mogamulizumab (Poteligeo, Kyowa Kirin) and obinutuzumab (Gazyva, Roche).

- High levels of β-1,4 galactosylation on the Fc glycans of mAbs enhance their complement-dependent cytotoxicity (CDC) (13) and ADCC (14). High β-1,4 galactosylation is, therefore, a preferable attribute of oncolytic mAbs.
- High levels of α-2,6 sialylation have been linked with enhanced anti-inflammatory activity in intravenous immunoglobulin (IV Ig) therapies (15) and would, thus, be a desirable attribute of immune-modulating TGPs, such as adalimumab (Humira, AbbVie) and Enbrel. Importantly, the anti-inflammatory properties of siaylation are exclusive to the glycosidic bond conformation (α-2,6) and the sialic acid species (N-acetylgalactosaminic acid, Neu5Ac) involved (15). CHO, NS0, and Sp2/0 cell lines only produce α-2,3 bonds and may also produce siaylation with N-glycolyl neuraminic acid (Neu5Gc), a moiety that may be immunogenic in humans (16). Higher Neu5Ac siaylation has also been reported to increase the serum half-life of TGPs (17).

Protein glycosylation in mammalian cells

Protein asparagine (N)-linked glycosylation occurs in two steps (18). The first occurs while the protein is being synthesized in the endoplasmic reticulum and entails the covalent addition of a large unprocessed precursor oligosaccharide to asparagine residues of the protein backbone. The glycoprotein is then transferred, via vesicles, to the Golgi apparatus, where the second and final step of the N-glycosylation process occurs: while transiting through Golgi, the protein-bound glycan is sequentially modified by several enzyme-catalyzed carbohydrate removal and addition reactions.

Serine/threonine (O)-linked glycosylation occurs entirely in the Golgi apparatus and begins with the addition of N-acetylgalactosamine (GalNAc) to serine or threonine residues on the protein backbone (19). After this first step, the glycan is modified by a sequence of enzyme-catalyzed monosaccharide addition reactions that extend its branching and length (19). CHO cells produce only two O-glycosylation variants, which consist of the mono- and bi-sialylated ‘Core 1’ structures shown in Figure 1 (20).

For the purposes of this review, the glycosylation process is considered to have two distinct inputs. The first encompasses the enzymes, which catalyze the monosaccharide removal and addition reactions (glycoenzymes). The second input for the glycosylation processes consists of nucleotide sugar donors (NSDs), which are metabolites that provide monosaccharides for the sugar addition reactions of the glycosylation process. NSDs are endogenously synthesized by the production cell lines using common nutrients, such as glucose and glutamine, as substrates (21). Thus, NSDs are the direct link between cellular metabolism (i.e., nutrient availability) and TGP glycosylation. Many cell culture NSD precursor feeding strategies have been developed to tune TGP glycosylation (22,23).

Models of therapeutic protein glycosylation (2009 to 2019)

The first model for N-glycosylation, published in 1996, aimed to describe the addition of glycans to the peptide backbone of proteins (24). From then, N-glycosylation models expanded to include the extent of glycan processing within the Golgi apparatus, thus aiming to depict the variability observed in TGP glycosylation profiles. Descriptions of glycosylation soon required strategies for automatically generating the complex reaction networks involved in the process and were pioneered by Krambeck and Betenbaugh in 2005 (25). Building on these seminal studies, more than 20 mathematical models for protein glycosylation have been developed to date. Based on structure and solution strategy, the mathematical models of TGP glycosylation can be grouped into three categories: kinetic models, flux-based models, and statistical models.

Kinetic models attempt to capture the time-dependent mechanisms underlying glycosylation and are based on dynamic material balances for all TGPs and NSDs present in Golgi (26–28). Given the inherently dynamic nature of cell culture processes, kinetic models are particularly suited to describe the effects bioprocess conditions have on TGP glycosylation. A fundamental drawback of kinetic models is that they require a substantial amount of experimental data to determine robust values for their unknown parameters (e.g., enzyme kinetic rate constants).

Flux-based glycosylation models consist of material balances for all TGPs present in the Golgi apparatus and are built using reaction networks that define the production and consumption stoichiometry of each species. To solve flux models, steady state is assumed, and the resulting system of linear equations is solved for the rates (fluxes) at which all TGPs are interconverted. Because the resulting system of linear equations is usually underdetermined (more unknown fluxes than equations), flux models must be solved using constraint-based linear programming (29,30) or probabilistic methods, such as Markov chain Monte Carlo simulations (31,32).

A key advantage of flux-based models is that their solution requires reduced amounts of experimental data. The main drawback of flux-based models is that their solution inherently assumes steady-state, which limits their ability to describe the dynamic shifts in TGP glycosylation often observed in cell culture processes. This limitation has been recently addressed by including parameters representing dynamic shifts in TGP residence time within Golgi (30).

Statistical models are abstract black-box mathematical representations where process inputs are quantitatively related, via statistical regression strategies, with TGP...
glycosylation profiles. Examples of statistical models of TGP glycosylation are design of experiment (DoE) surface response models (23) and partial least squares regression (33,34). Advantages of statistical models are that they do not require a priori knowledge of the process, require little or no end-user modeling expertise, and can therefore be deployed with relative ease. Statistical models are limited in that they are exclusively data-driven and, thus, are unable to yield insight into the mechanisms underlying TGP glycosylation. Furthermore, the predictive capability of statistical models may break down if model inputs drift outside the input space with which they were calibrated.

Table I presents the glycosylation models that have been developed since 2009 and highlights how each model has been used toward potential TGP quality assurance applications.

**Deployment of glycosylation models for biopharmaceutical QA**

Table I shows that all published glycosylation models have been used for applications that can directly support TGP QA practices. Four QA application areas stand out: (i) data analytics, (ii) bioprocess characterization, (iii) cell line engineering/development, and (iv) manufacturing bioprocess optimization and control (21,23,26,27,29–48).

Kinetic models appear to be the most versatile, having been used for all four application areas. Flux-based models have mainly focused on cell line selection and glycoengineering, and statistical models have been used for bioprocess characterization, control, and optimization. The application areas for the different modeling strategies results from their underlying features. Because kinetic models aim to mechanistically describe the glycosylation process, they are capable of covering all QA application areas. Flux models are well-suited to define cell glycoengineering strategies because they focus on the rates of glycoenzyme-catalyzed reactions. By definition, statistical models quantitatively represent correlations between bioprocess conditions and TGP glycosylation. Therefore, they are particularly adept for bioprocess control and optimization QA applications when mechanistic bioprocess knowledge is lacking.

Although the deployment of statistical models in industry is increasing at an accelerated pace (49), the use of mechanistic glycosylation models remains to be widespread. This disparity may arise from the use of specialized software and the perceived need for expert user input associated with mechanistic modeling. Despite these challenges, mechanistic models are, conceptually, more versatile than their statistical counterparts because they are based on the biochemical mechanisms underlying the glycosylation process. An interesting example where these limitations are addressed is the GLYMMER (ReaTech) software platform, which is based on the work by Bennun et al. (37), runs on Microsoft Excel, and requires only moderate user input and expertise.

**Conclusion**

The deployment of different glycosylation modeling strategies depends entirely on the TGP quality assurance application they will be used for. Statistical models can be readily deployed in the industrial setting for bioprocess design, control, and optimization (33,43) with minimal user input and expertise. Mechanistic models (kinetic and flux-based) have been shown to be particularly robust for cell line characterization (27,50) and glycoengineering (26,31) as well as for bioprocess design and optimization (42,47).

To fully exploit the advances in glycosylation modeling toward the develop-
ment, control, and optimization of next-
generation TGP production bioprocesses,
close collaboration between academic
and industrial groups must continue so
that the models are fit for purpose and
require minimal end-user expertise for
deployment.

### References


### Table I. Mathematical models of protein glycosylation (2009–2019).

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Model type</th>
<th>Therapeutic glycoprotein (TGP) glycosylation quality assurance (QA) applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krambeck et al. I (35)</td>
<td>2009</td>
<td>Kinetic</td>
<td>Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) glycan data analysis for cell line characterization.</td>
</tr>
<tr>
<td>del Val et al. (36)</td>
<td>2011</td>
<td>Kinetic</td>
<td><em>In-silico</em> cell line glycoengineering.</td>
</tr>
<tr>
<td>Bennun et al. (37)</td>
<td>2013</td>
<td>Kinetic</td>
<td>MALDI-TOF glycan and transcriptomic data analysis for cell line characterization.</td>
</tr>
<tr>
<td>Grainger &amp; James (23)</td>
<td>2013</td>
<td>Statistical</td>
<td>Design of experiments (DoE) surface response model for at-line bioprocess control.</td>
</tr>
<tr>
<td>Ohadi et al. (38)</td>
<td>2013</td>
<td>Kinetic</td>
<td>Predicts dynamic variations in monoclonal antibody (mAb) glycans for bioprocess characterization.</td>
</tr>
<tr>
<td>Jedrzejewski et al. (21)</td>
<td>2014</td>
<td>Kinetic</td>
<td>Predicts dynamic variations of mAb glycans from extracellular nutrient availability for bioprocess characterization.</td>
</tr>
<tr>
<td>Hang et al. (29)</td>
<td>2015</td>
<td>Flux-based</td>
<td>Glycan data analysis for protein and cell line characterization.</td>
</tr>
<tr>
<td>del Val et al. I (26)</td>
<td>2016</td>
<td>Kinetic</td>
<td>Predicts dynamic variations of mAb glycans for bioprocess characterization, cell line selection and <em>in-silico</em> glycoengineering.</td>
</tr>
<tr>
<td>del Val et al. II (39)</td>
<td>2016</td>
<td>Reconstruction</td>
<td>Defines the nucleotide sugar donor (NSD) demand towards cellular glycosylation for cell line characterization and bioprocess control.</td>
</tr>
<tr>
<td>McDonald et al. (40)</td>
<td>2016</td>
<td>Reconstruction</td>
<td>Automated framework for O-glycosylation reaction network reconstruction for cell line characterization.</td>
</tr>
<tr>
<td>Spahn et al. (31)</td>
<td>2016</td>
<td>Flux-based</td>
<td><em>In-silico</em> Chinese hamster ovary (CHO) cell line glycoengineering.</td>
</tr>
<tr>
<td>Villiger et al. (41)</td>
<td>2016</td>
<td>Kinetic</td>
<td>Predicts dynamic variations of mAb glycans from cell culture conditions for bioprocess characterization and control.</td>
</tr>
<tr>
<td>Hutter et al. (30)</td>
<td>2017</td>
<td>Flux-based</td>
<td>Predicts dynamic variations of mAb glycans from manganese supplementation for bioprocess characterization and control.</td>
</tr>
<tr>
<td>Karst et al. (42)</td>
<td>2017</td>
<td>Kinetic &amp; Statistical</td>
<td>Compares kinetic and statistical models for perfusion bioprocess optimization and control.</td>
</tr>
<tr>
<td>Krambeck et al. II (27)</td>
<td>2017</td>
<td>Kinetic</td>
<td>MALDI-TOF glycan and transcriptomic data analysis for cell line characterization and <em>in-silico</em> cell line glycoengineering.</td>
</tr>
<tr>
<td>Sokolov et al. I (43)</td>
<td>2017</td>
<td>Statistical</td>
<td>Used to design cell culture media to achieve glycosylation biosimilarity of a mAb (bioprocess optimization and control).</td>
</tr>
<tr>
<td>Sokolov et al. II (34)</td>
<td>2017</td>
<td>Statistical</td>
<td>Predicts dynamic variations of mAb glycans from cell culture conditions for bioprocess characterization and control.</td>
</tr>
<tr>
<td>Sou et al. (44)</td>
<td>2017</td>
<td>Kinetic</td>
<td>Predicts dynamic variations of mAb glycans from cell culture conditions for bioprocess characterization and control.</td>
</tr>
<tr>
<td>Spahn et al. (32)</td>
<td>2017</td>
<td>Flux-based</td>
<td><em>In-silico</em> CHO cell line glycoengineering for glycosylation biosimilarity.</td>
</tr>
<tr>
<td>Aghamohseni et al. (45)</td>
<td>2017</td>
<td>Kinetic+flux-based</td>
<td>Predicts galactosylation from cell culture conditions for bioprocess characterization and control.</td>
</tr>
<tr>
<td>Kremkow &amp; Lee (46)</td>
<td>2018</td>
<td>Flux-based</td>
<td><em>In-silico</em> CHO cell line glycoengineering.</td>
</tr>
<tr>
<td>Sokolov et al. III (33)</td>
<td>2018</td>
<td>Statistical</td>
<td>Predicts dynamic variations of mAb glycans from cell culture conditions for bioprocess characterization and control.</td>
</tr>
<tr>
<td>Kotidis et al. (47)</td>
<td>2019</td>
<td>Kinetic</td>
<td>Used to design an optimal NSD precursor feeding strategy that maximizes mAb galactosylation while maintaining product titer.</td>
</tr>
<tr>
<td>Le et al. (48)</td>
<td>2019</td>
<td>Reconstruction</td>
<td>Automated framework for O-glycosylation reaction network reconstruction/visualization for cell line characterization.</td>
</tr>
</tbody>
</table>
Despite there being various terms used, counterfeit, falsified, fake, and so on, a drug that has been fraudulently manufactured and distributed to mimic an authorized medicine, whether branded or generic, poses significant risks to companies and, more importantly, to patient health. The World Health Organization (WHO) estimates that one in 10 medical products are standard or falsified in low- to middle-income countries, based on a literature review of previously published papers (1).

In financial terms, as reported by Strategy&, PricewaterhouseCoopers' strategy consulting business, falsified medicines represent a lucrative portion of illicit goods sold within the global market, estimated to range from €150 billion to €200 billion (US$163 billion to $217 billion) per year (2). Given the size of the market and the risk to patient health, many authorities have been implementing regulations to protect the security of the supply chain.

“The proliferation of online pharmacies, and the Internet in general, has meant that the pharmaceutical blackmarket has trickled into mainstream society and consequently become a widespread issue,” asserts Staffan Widengren, director corporate projects, Recipharm. “As a result, health regulators have established new legislation and surveillance strategies around supply chains in a bid to prevent and minimize the circulation of falsified drugs. Without supply chain security measures, we cannot effectively track or determine the legitimacy of a drug product.”

Security of the supply chain is critical for all companies that offer products and services to consumers, concurred Ettore Cucchetti, CEO of ACG Inspections, particularly in terms of counterfeit products, product damage or theft, and smuggling. “For the pharmaceutical industry, which is dealing with products and services directly impacting human health, supply chain security becomes more crucial in terms of a company’s product integrity, brand image, and, ultimately, its bottom line,” he says.

**Different approaches**

As Michael Pisa and Denise McCurdy reported in their policy paper in February 2019, at a basic level there are two traceability models that can be adopted (3). One model is to have a point-of-dispense verification approach where verification occurs at the top of the supply chain and then also at the bottom. The other model is full traceability, which is more complex in nature as the tracking and tracing of products occurs every time they change hands within the supply chain.

Many countries and regions have already signed a traceability approach into law, including China, India, Turkey, the European Union, and the United States, and approaches vary from country-to-country. “Verification and full traceability can both facilitate and improve supply chain security,” says Widengren.

The EU and US, for example, chose to adopt different approaches. The former employing the point-of-dispense verification approach while the latter is using the full traceability approach. “In the EU market, serialization requirements were implemented as part of the falsified medicines direc-
tive (FMD) regulation to protect the safety of patients,” adds Widengren. “Essentially, through serialization, dispensers gain the ability to verify product legitimacy before a drug reaches the patient by scanning the unique identifier included on the pack.

“Whereas, track-and-trace systems can not only determine the authenticity of a product at the point of dispense, but also track the movement of products and prohibit falsified medicines from progressing through the supply chain,” he continues. “Each partner involved in getting drugs to market can scan unique identifiers to access data around the journey of medicines and verify the authenticity of medicines as they move through the supply chain.”

Dealing with data
Each traceability approach being implemented across the world has inevitably impacted industry, in particular as a result of the need to deal with vast amounts of data. “Due to the sheer amount of data generated by serialization requirements, organizations have been required to evaluate and adopt software technology solutions to create, capture, store, report, and share compliance data at scale,” notes Martin. “This question of technology scalability remains a real concern when it comes to simply meeting the requirements of these legal mandates themselves, which is one of the critical reasons that a cloud-based, network platform is optimal,” he continues.

In agreement, Widengren states that cloud-based networks have been found to be the most successful in terms of connecting supply chain partners and enabling the exchange of serialization data. “As well as enabling compliance with serialization regulations, these platforms also offer the opportunity for businesses to improve supply chain visibility and gain additional value from their investment,” he says. “By giving companies greater insight into their operations, businesses can make more informed decisions in areas such as supply and demand forecasting, product recalls, and even achieve engagement with patients.”

Additionally, Martin emphasizes that as industry looks to the future and leveraging the data gained from serialization, there will be a shift away from the fragmented silo nature of the bio/pharma supply chain that has existed previously as a fractious supply chain hinders visibility and impacts performance. “Instead, serialization should be used as a lens to look at the end-to-end digital supply chain and, if done right, will lead to transformative benefits in terms of increasing business value through more collaborative supply chains and end-to-end visibility into value networks,” he explains.

“Blockchain will be considered as one of the critical factors when it comes to selecting a supply chain partner in the future,” adds Cucchetti. “Product traceability and recalls are known to be the biggest challenges for most industries, and blockchain landscape can be used to secure the transaction between the supply chain partners. With blockchain, companies can address counterfeit issues through the authentication process, and they can perform product recall smoothly. This can help them to identify the issues in logistics and distribution channels, using the complete supply chain data to optimize the supply chain.”

Regulatory initiatives
“Regulatory and government bodies are looking into all available and emerging technologies for securing supply chains,” notes Ettore Cucchetti. “Each regulatory body has multiple objectives, but the preliminary goal remains the same—to secure the product from manufacturer to end consumer.”

Giving some examples, Cucchetti highlights Russia, which has mandated crypto tail into barcoding processes; Indonesia, which is assessing product authentication techniques; and the US, which is looking to evaluate blockchain with serialization. “Currently, most of the regulatory requirements are focused towards serialization and track and trace, as well as mandates for the pharmaceutical industry,” he says. “Going forward, it is likely that similar regulations will be applicable to all other industries as well. Government and regulatory bodies will be more stringent in regulation—considering consumer health and safety requirements. As the technologies evolve, each government will be evaluating possible technological implementations to secure supply chains to fight against counterfeiters, and also to have complete visibility of the industry.”

Specifically focusing on the US and its exploration of methods to enhance the safety and security of the supply chain, Martin discusses FDA’s Drug Supply Chain Security Act (DSCSA) pilot program. “Recently, FDA announced a pilot program project...
Companies should always be mindful of the landscape is in a state of flux,” emphasizes Widengren. “It is essential to consider long-term prospects so that a plan can be made around new legalities. As such, pharmaceutical manufacturers should invest time into understanding the markets they operate in, as well as the ones they may potentially pursue. This way they can design a strategy that will help facilitate market entry and progression with as little complexity and limitation possible.”

For Cucchetti, a proactive approach to supply chain security is key as it can afford companies time to be able to adapt to all changes required when complying with regulations. “Companies should form a dedicated team with all business functions involved in the serialization project, documenting all regulatory and business requirements,” he says. “At all times, organizations should work alongside the implementation partner and possibly with the regulation bodies to understand the upcoming changes and work towards accommodating them.”

As a final note, Widengren explains that for companies to be able to reap the benefits of supply chain security requirements and for optimum preparedness and future safeguarding, companies should consider implementing aggregation capabilities. “Aggregation is not always a mandatory measure,” he summarizes, “but it is expected to become part of legislative requirements in the future.”

References

Like many crucial regulations, good laboratory practices (GLPs) were enacted in 1979 after FDA observers found serious problems in documentation, training, and data integrity at a number of research labs (1). Global GLPs establish guidelines for standard operating procedures (SOPs), which explain how to carry out specific tests and how to use and maintain laboratory equipment. GLPs also set requirements for equipment calibration and maintenance, data collection, and investigation and documentation of out-of-specification (OOS) findings.

Decades later, global regulators still find deficiencies in the way that some companies’ preclinical and quality-control labs approach data integrity, training, and SOPs. Incorrect approaches to investigating OOS conditions are also frequently found in regulatory citations, for GLPs as well as for good manufacturing practices (GMPs).

**Lack of reproducibility**
Another major problem that can be traced to inadequate compliance with GLPs is lack of reproducibility (i.e., a situation in which other laboratories cannot replicate the results published in original research conducted in an innovator laboratory). In 2015, the Global Biological Standards Institute (GBSI) found that 50% of published preclinical research could not be reproduced, a problem that continues to delay the development of new products and wastes $28 billion/year in the United States alone (2).

In some cases, researchers found, equipment was not being used efficiently based on vendor guidelines; in others, biological reagents and reference materials, cell lines, antibodies, and reagents were not properly validated (3). Also faulted were incomplete study data and lab protocols.

**Improving data access**
Industry executives have pointed to cross-functional data access and utilization as a major challenge for the industry. This challenge affects the lab as well as the plant. IDC Health Insights surveyed 126 biopharmaceutical and pharmaceutical executives in the United Kingdom and the US, and found a significant gap between their need and their strategies for harnessing data (4). More than 98% of respondents said that cross-functional data access was important or very important to their business strategies, and 94% described the ability to apply advanced analytics and/or artificial intelligence the same way. However, 51% of those surveyed said that they did not have a clear strategy in place to help them reach either of those goals.

A number of digital tools are available to help lab scientists capture and use more data, to improve laboratory efficiency and reproducibility. These tools allow data to be extracted from various software systems, and some of them feature use of machine language and elements of artificial intelligence. One example is LabStep, an interactive digital platform designed to help scientists get around some of the deficiencies of electronic lab notebooks (ELNs). The platform allows users to refer directly to the most relevant protocols, SOPs, and other important data (5) as they work.

LabTwin is also active in this area, and will introduce a new voice-activated lab assistant at BIO 2019 in June.
in Philadelphia. Combining artificial intelligence, voice recognition, and machine language, the hands-free device allows researchers to document steps they have taken and to save explicit details that cannot currently be saved in ELNs (6). Labfolder (7) is yet another platform that has been designed to enable more laboratory data to be saved, accessed, and used throughout any organization.

“*It is important to involve the sample analysis team in performing some, if not all, of the validation experiments, with technical assistance provided by the R&D scientists who developed the method.*

— Stuart Jones, PPD Laboratories

Ultimately, compliance with GLPs depends on following best practices. Stuart Jones, regulatory quality assurance professional in good laboratory practice (RQAP-GLP) and director of quality assurance at PPD Laboratories’ Bioanalytical Laboratory shared recommendations with *Pharmaceutical Technology.*

**Best practices**

**PharmTech:** What GLP problems do you frequently encounter at pharma and biopharma companies, and how can they be prevented?

**Jones:** Because we work in such a regulated environment, a seemingly minor matter can have a significant impact on quality. As such, training is an important best practice, from the time of hire, to retraining when a deviation occurs.

Annual refresher training as well as specific group remedial training should also be provided whenever needed. Meanwhile, the use of automated or electronic systems, such as laboratory e-notebooks, can be especially beneficial in maintaining the most accurate documentation.

**PharmTech:** How do you recommend that biopharmaceutical companies tackle training?

**Jones:** Initial training, especially with newer employees, can be done through reading, lecture, and/or some type of knowledge or learning assessment, but the best results occur when that theoretical work is followed up and supplemented by hands-on training. This is accomplished most effectively by teaming new employees with experienced staffers, using training goals established within a predetermined curriculum.

Some measure of refresher training should be required on at least an annual basis and it should be consistent across all experience levels. Metrics generated around unplanned protocol and SOP deviations, as well as human error, should be used as indicators in determining the course and effectiveness of current training plans.

**PharmTech:** What best practices do you recommend to make data less siloed and more accessible to those who may need it (on cross functional teams?)

**Jones:** One of the best ways to establish a more cross-functional approach and enhance data accessibility is to use one system across all sites. If one across-the-board system is not possible, then the multiple systems must be able to work in tandem. Data portals and SharePoint sites also can be utilized to securely share information on a real-time basis.

**PharmTech:** Reproducibility is a major problem for biopharmaceutical preclinical research. Is this problem also seen in pharma quality control labs? What best practices do you recommend regarding the validation of materials and methods?

**Jones:** We have found that, after research and development of the method by our R&D scientists, it is important to involve the sample analysis team in performing some, if not all, of the validation experiments, with technical assistance provided, as needed, by the R&D scientists who developed the method. This approach allows for a shared collaboration between the research and production teams, and continues into sample analysis to ensure reproducible results from the developed and validated method.

Best practices include following the proper bioanalytical method validation guidances; the bridging of critical reagents; analyst method qualification and scientific expertise/knowledge of the assay; as well as the use of incurred sample reproducibility testing as one of the ways that the bioanalytical lab can prove that the method can be reproduced.

**References**

Taking the time to establish a quality agreement and investigate the details of their OOS procedure is the first step in establishing a good working relationship with your contract test laboratory. This working relationship will become invaluable when an OOS occurs. The final product testing procedure for OOSs isn’t the only one you need to review, however. You should also look at the quality agreement and OOS procedure being used by your manufacturer for in-process test results, assuming they are different entities. The same information required in the final product OOS procedure should be the same for in-process testing.

References
1. 21 CFR 200.10 (b)

Your opinion matters. Have a common regulatory or compliance question? Send it to shaigney@MMHGroup.com and it may appear in a future column.
Quality Agreements and Out-of-Specification Investigations

A good working relationship between sponsor and contractor will become invaluable when an OOS occurs, says Susan J. Schniepp, executive vice-president of post-approval pharma and distinguished fellow, Regulatory Compliance Associates.

Q. I’m responsible for quality at a small, virtual startup company, and we contract out all of our activities. I’m working on documentation to contract out our product testing and was wondering what information there is regarding quality agreements and laboratory investigations.

A. The best place to start is to take a critical look at existing guidance documents and regulations that govern quality agreements and out-of-specification (OOS) investigations.

The basic philosophy when establishing any quality agreement is to understand that the contract provider and contract giver are partners and their behaviors reflect on each other. The 21 Code of Federal Regulations (CFR) 200.10(b) confirms this concept by stating: “The Food and Drug Administration is aware that many manufacturers of pharmaceutical products utilize extramural independent contract facilities, such as testing laboratories, contract packers or labelers, and custom grinders, and regards extramural facilities as an extension of the manufacturer’s own facility” (1). The next document to review for quality agreements is the FDA guideline titled Contract Manufacturing Arrangements for Drugs: Quality Agreements. Section B, Elements of a Quality Agreement, Part e. Laboratory controls states that a quality agreement should include: “Designation of responsibility for investigating deviations, discrepancies, failures, out-of-specification results, and out-of-trend results in the laboratory, and for sharing reports of such investigations” (2). This confirms that the responsibility for OOS investigations is shared and communication between the contract giver and contract provider is critical. The European Union also addresses the need for a relationship between you and your outsourced laboratory in EudraLex, Chapter 7 (7.15) on Outsourced Activities by stating: “The Contract should describe clearly who undertakes each step of the outsourced activity, e.g. knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis)” (3).

The above regulations establish the need for quality agreements that cover laboratory activities but doesn’t define what needs to be in an OOS procedure. The EU addresses the need to investigate OOSs in their GMPs. EudraLex Part 1, Section 6.35 states, “Out-of-specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, affecting product batches released on the market should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with Chapter 8 of the GMP Guide and in consultation with the relevant competent authorities” (4). Part 2 of the EU GMP guide for APIs states in section 11.15 that: “Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any re-sampling and/or retesting after OOS results should be performed according to a documented procedure” (5).

The best guidance, however, on conducting OOS investigations is the information provided in FDA’s Guidance for Industry, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production (6). The responsibilities for the laboratory analyst and supervisor are clearly defined in this guidance and should be reflected in any laboratory OOS procedure. A well-written standard operating procedure (SOP) on OOSs should require investigations to be thorough, timely, unbiased, well documented, and scientifically sound. Often, the procedure will contain a checklist that assists in identifying obvious laboratory errors. The checklist assesses the suitability of analyst qualification and training, use of correct procedure and specification, the calibration and performance of the equipment, correct preparation of test solutions and dilutions, use of proper reagents and standards, calculations, etc. A thorough checklist and analyst documentation are critical in identifying true laboratory error. The SOP should also discuss the sample retesting requirements when a true laboratory error is determined to be the cause of the OOS.

The most important and critical element for OOS investigations is specifying the timeliness. This should be stipulated in the SOP and, in most cases, the investigation into the OOS, from the laboratory perspective, should be concluded in 24 hours or less. The expectation of when the contract lab will inform you of any OOS obtained should be clearly defined in your quality agreement. The sooner a laboratory error can be ruled out as the cause of the OOS result, the sooner the full-blown manufacturing investigation can be started.
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