Putting the Patient at the Heart of Dosage Design

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Dosage form priorities are shifting to focus on user-friendliness, leading to greater engagement with outsourcing partners earlier in development timelines.

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n research laboratories around the world, thousands of compounds are being studied as potential drugs to treat cancers, infectious and chronic diseases, and other conditions. The route of delivery for the therapy is always a crucial choice, tied to the characteristics of the molecule, its solubility, and complexity.

Advances in drug delivery devices for injectable and inhalation drugs—as well as new oral solid dosage forms, such as orally-dissolving tablets and new capsule forms—provide drug formulators with tools for producing better, more effective therapies. More importantly, these new drug dosage forms provide more options for patients, potentially improving not only the effectiveness of their treatments, but their adherence to dosing regimens. Read the cover story, “Putting the Patient at the Heart of Dosage Design,” to learn about recent trends in dosage form technologies and strategic approaches to place the needs and desires of patients at the center of drug development efforts.

Improving on existing drug formulations—especially oral solid drug products—to improve solubility is a common, but challenging practice. A feature article in the Development section of this issue, “In-Vivo Demonstration of Enhanced Bioavailability of Acalabrutinib ASD Tablets,” discusses how amorphous solid dispersions can increase drug solubility and maximize the amount of drug that reaches the bloodstream, improving the effectiveness of orally-delivered drugs.

Such challenging formulation projects often require bio/pharmaceutical companies to seek external expertise from contract development and manufacturing organizations (CDMOs) to provide the technologies, testing, and/or staffing not available internally. In “Developing the Best Formulation Partnership,” in the Outsourcing section, a panel of experts from CDMOs share insight on industry trends, common requests, biggest challenges, and benefits of outsourced formulation services.

In recent years, FDA-issued warning letters have detailed the consequences of poor data management practices at bio/pharmaceutical facilities and supporting suppliers. With data generated and reported from many sources, risk-based practices to ensure the validation of the information are essential. This month’s Quality/Regulatory feature, “Implementing Data Integrity Compliance in a GLP Test Facility,” examines a case study of how data from a building management system can be used to monitor environmental and storage conditions and how the records can be made compliant with regulatory requirements. Recommendations for applying ALCOA+ principles—attributable; legible and permanent; contemporaneous; original record; accurate; and complete, consistent, enduring, and available—are shared.

The evolving nature of bio/pharmaceutical manufacturing technology is illustrated in the article “Designing Incubators for Cell Therapy Manufacturing,” an analysis of incubator conditions needed for cell therapy manufacturing, in the Manufacturing section of this issue.

Mike Hennessy, Sr.
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As the global COVID-19 pandemic passes the 18-month mark, there are signs that some businesses are resuming pre-pandemic operations. Answers to the “when can I …” questions about returning to the office, school, vacation, indoor activities vary based on region and vaccination status. On the bio/pharmaceutical front lines, drug companies and Congress are asking FDA: When will inspections resume?

In March 2020, travel restrictions prompted FDA to put inspections on hold and conduct only mission-critical inspections and focusing on efforts to prevent drug shortages and bring pandemic-related vaccines treatments to market. From March 2020 to March 2021, application decisions of 48 human drugs—including six deemed “mission critical” and nine animal drugs were delayed because inspections were not conducted.

As of March 2021, the agency had a backlog of approximately 1000 inspections for human and animal drug facilities to tackle (1).

In a six-page letter dated July 22, 2021, members of the House Energy and Commerce Committee sought details about foreign inspections; if delayed inspections are slowing the approval of applications for new drugs, generics, and biosimilars; if FDA is using inspection reports from trusted inspectorates; and how will FDA’s data modernization plan impact inspection activities. In addition, the committee asked how the $38.3 million provided to FDA to address the pandemic has been used to resume domestic and foreign inspections (2).

Acting FDA Commissioner Janet Woodcock outlined the Agency’s plans in testimony before the Senate Health, Education, Labor and Pension Committee on July 20, 2021 (3). FDA has established an Inspectional Oversight Resiliency Roadmap for FDA Inspectional Oversight (4). The House Committee’s letter closed with the question: How long, after return to standard operations for domestic and foreign inspections, will it take to clear the backlog? As in other aspects of businesses and daily life, the desire to make up for lost time is urgent.

References
Is Your Company Ready for a Remote Audit or Inspection?

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Eppendorf has redesigned the CryoCubeF440 ultra-low temperature freezer class to be more sustainable by improving performance and incorporating eco-friendly cooling liquids and insulation foam.

The new freezer saves up to 23% of power and offers 30% more space relative to previous models, the company reports. A temperature of -80° C can be reached in 200 minutes; energy consumption at this temperature is 6.8 kW/h per day.

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The ROSS Model CDA-25 (pictured) includes dry-running Double FlexiLip seals on both agitator shafts, making it appropriate for vacuum operations up to 29.5” Hg. This model also features a portable mixing vessel with heating/cooling jacket.

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As federal officials struggle to boost US vaccination rates to combat the coronavirus pandemic, manufacturers and regulators are responding with efforts to file and evaluate biologics license applications (BLAs) for COVID-19 vaccines to further assure the public of product effectiveness and safety. The rise of COVID variants has made public health officials anxious to expand immunity more widely and quickly in areas with low vaccination rates, and experts hope that full approval of existing and new vaccines will increase public confidence in their value.

The top priority for the Center for Biologics Evaluation and Research (CBER) is to approve BLAs for COVID vaccines to address vaccine hesitancy, said CBER Director Peter Marks. He emphasized that the agency is working to “move this forward” as quickly as possible in remarks at the Drug Information Association (DIA) virtual annual meeting on June 30, 2021. Even if full approval encourages only 5% more individuals to get vaccinated, “that will make a difference,” he observed, adding that “having an approved vaccine may help.”

FDA won plaudits this past year for devising a clear and pragmatic process for awarding Emergency Use Authorization (EUA) for COVID-19 vaccines able to meet high standards for product safety and efficacy. Although the three vaccines with EUAs have experienced few adverse events and have provided clear protection against infection for much of the population, strong vaccine hesitancy is limiting efforts to expand these gains. With variants and another wave of COVID-19 infections threatening (or emerging), FDA officials recognize that full BLA approval may help counter concerns about the “experimental” nature and limited testing of the available preventives.

To move forward, Pfizer initiated a rolling submission of a BLA on May 7, 2021, initially filing existing preclinical and clinical information, with manufacturing and facility data to come. On July 16, 2021, FDA formally accepted the company’s BLA for individuals age 16 and older and granted the application priority review (1). Moderna announced on June 1, 2021, that it also had launched a rolling BLA submission, with an eye to gaining priority review and approval by year-end (2). FDA acknowledges that BLAs require more information than the initial EUAs, including data from conformance lots, full characterization reports, additional facility inspections, closer scrutiny of individual safety cases, and more follow-up on adverse events. Marks explained in a letter to The New York Times on July 9, 2021, that CBER staff can’t turn around such evaluations in a few weeks but will require several months to fully assess the complete data (3). Marks emphasized that the review of applications for full approval of COVID-19 vaccines is “one of the highest priorities” at FDA, but that the extensive additional manufacturing and clinical information warrants a “high-quality review” to avoid undermining the public trust in the agency.

Even so, some public health authorities have criticized FDA for moving too slowly in processing the BLAs, while others agree with Marks that any appearance of hasty action or incomplete oversight may only aggravate latent fears.

Future efficiencies
In planning for more efficient and effective vaccine development for the next epidemic or pandemic, FDA and manufacturers agree that master protocols would be helpful, as would the early designation of a single central laboratory to handle testing and assays across different platforms. A valid concern is that each of the approved vaccines from Moderna, Pfizer-BioNTech, and Johnson & Johnson was tested and developed using different endpoints for vaccine manufacturing, one needs productive facilities that can shift from “slow simmer” to “low boil” very quickly.
and assays and without head-to-head comparisons. At the DIA meeting, Marks acknowledged that early on there was consideration of establishing a master protocol to test three or four initial vaccine candidates with one control group, but that timing issues prevented that approach. Waiting for all manufacturers to be ready for clinical studies would have delayed product approvals for three or four months, he explained, which most likely would have increased COVID deaths.

Marks also cited the need for better strategies to quickly scale up vaccine production, acknowledging that manufacturing drug substance and drug product is “a huge issue.” That doesn’t mean building more plants to have them sitting there until needed, Marks said. For vaccine manufacturing, one needs productive facilities that can shift from “slow simmer” to “low boil” very quickly. Here advanced manufacturing methods may be important, with disposable and modular systems that can be easily transported to support production on a global basis. And although vaccine manufacturing requires considerable expertise, semi-automated processes would be more scalable and require a smaller, but still highly skilled, cadre of workers.

Manufacturers also are looking for more common guidance and requirements from regulators around the world.

Manufacturers are also looking for more common guidance and requirements from regulators around the world, and less “global disharmony” in policies and standards. Marks and others acknowledged that regulators could do more to come together and avoid claims that their vaccine is better than others. An initial area for collaboration may involve determining the need for COVID vaccine boosters or new preventives for variants. There also is interest in agreeing on what tests or measures would support boosters and or the need for annual COVID-19 vaccines.

Conversely, Marks noted, different authorities working at cross purposes and promoting diverse claims will only spur vaccine hesitancy and may delay efforts to bring the pandemic to an end.

References
Dosage form priorities are shifting to focus on user-friendliness, leading to greater engagement with outsourcing partners earlier in development timelines.

Research investment in the global biopharmaceutical market helps to drive innovation and development of novel therapeutic products to treat many diseases and illnesses. According to recent figures highlighted by the International Federation of Pharmaceutical Manufacturers and Associations, there are currently more than 8000 compounds in development around the world (1).

“A recent market report has shown that there was an influx of new products in the pipeline at all stages of clinical development during the 2020/2021 period (2), especially of early-stage clinical products,” notes William Chin, manager, global scientific affairs, Catalent, citing recent research studies. “Moreover, cancer, infectious diseases, and diseases of the central nervous system came up as the top areas of clinical trial activity last year. The number of people suffering from these chronic conditions is expected to rise as population growth is anticipated in many developing countries (3). The development of complex dosage forms is also expected to grow in parallel to increased diversity in the drug pipeline.”

Key trends
Over the past five to 10 years, the low water solubility of new molecular entities (NMEs) has been a major drug product development challenge, emphasizes Julien Lamps, product manager, Lonza Capsules and Health Ingredients. “Knowing the solubility performance attributes for the compound is important as it will aid selecting the right dosage technology,” he says.

“There have been numerous developments and innovations in drug delivery over the last few years to overcome challenges with products and formulations, such as biologics and complex entities like larger molecules,” adds Jnanadeva Bhat, head—formulation R&D (Pharma and Nutra), ACG Group. “Other trends that have evolved are pre-filled syringes, wearable injectors, and needleless syringes, each of which have a niche market.”

Considering the route of delivery, Chin states that injectable dosage forms are dominant in the development pipeline. “The intravenous route [is] seen to offer more advantages in early-stage studies as a means to quickly deliver the desired concentration of drug to the target via systemic circulation, and to achieve the required pharmacological response,” he confirms. “However, simply having injectables may no longer be sufficient anymore because of the growing demand for more patient-friendly formats, such as oral solid dosage (OSD) forms.”

Bhat concurs that even though the sector for specialty products has
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Cover Story: Drug Dosage Form Trends

witnessed growth, OSD forms have remained steady throughout the past decade. “There is demand for continuous innovation to improve efficacy, efficiency, and competence in [oral solid] dosage forms,” he says. “Developing novel and more efficient oral delivery routes also helps brands reach a larger audience. Thus, development scientists prioritize OSD forms because not only are they key to patient compliance, but they also have broad application.”

Over the past five to 10 years, the low water solubility of new molecular entities has been a major drug product development challenge. “Historically, they also have broad application.”

—Julien Lamps, Lonza Capsules and Health Ingredients

The growing demand for OSD forms has driven innovators to focus on patient-centricity early on in development, Chin continues. “This trend is especially true in the past year, where there has been an expectation to increase both the convenience of use and the therapeutic efficacy of the drug product, as well as ease of deployment without the need for cold-chain considerations, especially given the current focus on oral COVID-19 vaccine development,” he states.

“In biologics and small molecules, the trend shifted towards patient-centricity,” adds Tatiana Nanda, director and program leader, The Center for Breakthrough Medicines. “Historically, the sole focus for drug product development was effective treatment of the disease while now additional emphasis is put on patients experience and quality of life during treatment.”

Focusing priorities

“As innovators are focusing more on solutions that allow them to develop patient-centric drug products, the priorities of drug development are expected to not only demonstrate clinical efficacy and safety in patients, but also to address key challenges such as improving usability, bioavailability, stability, and palatability, while eliminating any variability due to food effects,” confirms Chin. As a result of this shift in priorities, advanced dosage forms, such as modified-release products, multiparticulates, ODTs, or new fixed-dose combinations, are increasingly in demand, he adds.

Dosage form priorities have certainly been adjusted. Lamps specifies, with the deployment of common strategies and platforms that help to enhance drug oral bioavailability, such as cosolvents, salts, surfactants, particle size reductions, polymorphs, lipid-based systems, amorphous solid dispersions, and so on. “Additionally, it is becoming a best practice to evaluate the end dosage form earlier in the development cycle,” he adds.

“Drug product design is more focused on meeting patient-centric target profiles and has become the goal for drug companies,” agrees Nanda. “Previously drug product profiles were a derivative of what upstream/downstream capabilities allowed. Now the selected profile and dosage form drive the required API process, needed concentration, and purity.”

The priorities of pharmaceutical companies have shifted as a result of the drive toward patient-centricity, Bhat concurs, with manufacturers seeking the most patient-friendly form that supports maximum therapeutic efficacy and safety of the formulation. “Regulatory bodies also encourage patient-centric dosage forms, which fuels this new focus,” he says.

Additionally, the change of priorities for development have led to the integration of patient-centric design early on in the development cycle, Bhat continues. “The physicochemical properties of an API usually point the formulator to the most suitable route of administration, as well as dosage form. The solubility of APIs specifies approaches for dose selection, excipient selection, and stability of the final product,” he says. “Bigger challenges are observed for larger molecule oral absorption, which need to be addressed adequately by formulation scientist.”

“Simply having injectables may no longer be sufficient anymore because of the growing demand for more patient-friendly formats.”

—William Chin, Catalent

Discussions between innovators and contract development and manufacturing organizations (CDMOs) on dosage form design are taking place relatively early on now, Chin states. Furthermore, manufacturability of the dosage form is being addressed earlier on by innovators, which is an aspect that has received less attention historically speaking, he notes. “Innovators have recognized that a druggable molecule alone does not automatically imply successful commercialization of a pharmaceutical drug product, but that there is also a need at an early stage to establish all other key considerations that will meet the target product profile covering patient and manufacturing requirements,” Chin says.

Taking patient opinions and assessments of dosage forms into consideration during design and development can also help to create user-friendly
products, Bhat highlights. As patient-centricity is becoming more prominent, so too are tailored dosage forms, which directs the industry away from a one-size-fits-all approach in terms of dosage forms, he explains. “With this trend, dosage forms will perform more effectively for individuals, and this is shifting pharma R&D towards new pathways,” Bhat says.

**Important innovations**

For Bhat, some of the most important innovations in drug dosage forms have been seen in the area of inhalation. “Local inhalation administration delivers sufficient levels of drug to the target organ, the lungs, while minimizing systemic exposure and side effects (primarily due to the reduced drug dose needed as compared to oral administration),” he says.

“Additionally, there is mounting interest in inhalation segment, where conventional molecules are converted into inhalation formulations,” Bhat continues. “In this area, dry powder inhalation formulations via hard capsules is a trend formulators and manufacturers are showing great interest in.

Capsules are not only robust and easy to use, but also help with effective delivery through the inhalation devices.”

“**Drug product design is more focused on meeting patient-centric target profiles.**”

—Tatiana Nanda, The Center for Breakthrough Medicines

Capsule-based dry powder inhalation (cDPI) formulations offer an affordable option that incorporate characteristics—such as reduced dosing frequency and side effects—and easy administration, which are preferable for patients, Bhat asserts. “The most impressive developments taking place in this field go beyond conventional respiratory therapeutic segments,” he says. “Many leaders are exploring cDPI for other therapeutic segments like Parkinson’s disease, migraine, tuberculosis, cystic fibrosis, and lung infection.”

Techniques, such as particle size reduction, spray-dried dispersions, and lipid-based formulation platforms, have helped overcome solubility-related issues, Lamps states. Additionally, as the techniques are complementary, they are applicable to a broad compound space, he says.

For large molecules, being able to reach high protein concentration and co-formulating with dispersion enhancers, such as hyaluronidase, has been a significant advancement, reveals Nanda. “[This innovation] allowed delivery of a high volume—up to 20 mL—of drug product as a single injection into subcutaneous space,” she stresses.

However, it is also important to consider innovation from the perspective of manufacturing, rather than just on new technologies that are centered on the discovery and development path, Chin emphasizes. “For example, one of our core expertise is in manufacturing softgel dosage forms for both immediate- and sustained-release,” he says. “With this capability-related issues, Lamps states. Additionally, as the techniques are complementary, they are applicable to a broad compound space, he says.

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In the future, demand for outsourcing will increase as the emergence of virtual and small biopharma companies continues, reveals William Chin, manager, global scientific affairs, Catalent. “Rather than using [contract development and manufacturing organizations] CDMOs to solely meet manufacturing requirements, innovators have become increasingly comfortable with engaging CDMOs in discussions on dosage form design, as they realize they can leverage a CDMO’s many years of expertise in formulation and manufacturing of dosage forms for multiple industry projects,” he says.

“Very frequently drug companies do not have sufficient resources to understand degradation mechanisms and develop the optimal drug product dosage form early in the development, resulting in cumbersome and complex preparation and administration of drug products in a clinical setting,” asserts Tatiana Nanda, director and program leader, The Center for Breakthrough Medicines. “Selecting an experienced CDMO partner with expertise in formulation, optimization of drug product, and robust and flexible manufacturing platform can resolve this issue.”

Traditionally, outsourcing partners focused on API development and manufacturing limited to standard fill/finish processes, Nanda continues. However, as advanced therapies have grown, the need for CDMOs that can provide unique specialized services to advanced therapies drug product development and manufacturing has been stimulated, she notes. “The demand for new products and innovations across all dosage forms necessitates the need for outsourcing for development and is an area that will likely see growth over the next few years,” adds Jnanadeva Bhat, head—formulation R&D (Pharma and Nutra), ACG Group. “Outsourcing not only gives flexibility in development, but also enables companies to meet the demand of new trends. In particular, there is a greater need for new products to be developed to meet patient-centric and individualized medicine requirements.”

Outsourcing plays a critical role in dosage form development, particularly in supporting the fast-track development of difficult-to-formulate new drug substances, confirms Julien Lamps, product manager, Lonza Capsules and Health Ingredients. “Considering partnering with companies that can handle products and equipment to enable formulation speed and innovation is definitely the path for growth in future,” he says. “However, in a world of exponentially growing knowledge, increasingly sophisticated technologies, and an uncertain economic environment, strategies in the field of outsourcing activities need to be set in a competitive and flexible way.”

—Felicity Thomas
modified-release applications. The typical development option for a modified-release softgel is through the formulation of the fill content followed by the coating of the capsules,” he says. By using a proprietary modified-release softgel capsule, which combines pectin and gelatin, a separate capsule coating step can be avoided, Chin adds.

“The capsule technology allows innovators to design the delayed-release profile to be incorporated directly into the softgel capsule shell, thereby making a separate capsule coating step unnecessary,” Chin continues. “This innovation reduces manufacturing time and yield loss and eliminates potential quality issues associated with coated softgels.”

**Market drivers**

“An important driver that could steer the dosage form market is the increasing demand for solutions that could overcome cold supply chain bottleneck constraints, especially given the current focus on vaccine development for COVID-19, as most vaccines are available as solution for injection that require ultra-cold chain storage,” Chin asserts. “A lot of effort and investment will be made to develop an alternative dosage form that could effectively deliver such biomolecules via the oral route. If this alternate dosage form could not only overcome enzymatic and permeability barriers, but also ensure stability and biological activity without the need for ultra-cold storage solutions, this could be expected to positively impact the global pipeline in the coming years.”

A rising demand for tailored or customized formulations and precision medicine will greatly impact drug dosage form development in the near future.

—Jnanadeva Bhat, ACG Group

In Lamps’ opinion, lipid-based formulations will continue to impact dosage form developments in the future by addressing the solubilization challenge. “As the technology maintains solubilization during the dispersion/digestion step in the gastrointestinal lumen, it’s favoring efficient diffusion through the mucus layer to reach the intestinal epithelium,” he explains.

Additionally, amorphous solid dispersions (ASDs), which dissolve rapidly to higher concentration than crystalline forms and maintain supersaturation in the intestine, promoting drug absorption, will impact dosage forms in the future, Lamps continues. “[ASDs] broad applicability, flexibility, and quenching rates makes them amenable for high-dose compounds,” he says.

A high priority effort for many drug developers is the creation of an appropriate dosage form for cell and gene therapies (CGT), Nanda specifies. “Formulation and manufacture of CGT drug products represents specific challenges not encountered by small molecules and biologics,” she says. “Early-phase clinical trials for advanced therapies are rather complex and include wide dose ranges. It becomes extremely important to introduce a proper, robust formulation for CGT therapies early on, to be able to accommodate an intended route of administration, indication, and dose level.”

Although CGTs are still only administered in a clinical setting, the requirement for an optimal dosage form is just as critical as it is for therapies (large and small molecule) that are administered at home, Nanda emphasizes. “Both healthcare professionals and patients greatly appreciate using a therapy that allows storage and shipment and convenient withdrawal for administration. Continued innovation of novel devices and adaption of existing platforms will also help enable advanced (tissue specific) therapy delivery.”

**References**

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A Digital Supply Chain Helps Ensure API Quality

Cynthia A. Challener

Ensuring API quality is essential to the safety of drug products based on small-molecule drug substances. That includes the quality of generic and branded APIs produced in-house or outsourced from contract manufacturers. The quality of raw materials, the quality culture and systems of API manufacturers, and other factors determine API quality.

Access to real-time or near-real-time supply-chain data through digitalization can help formulators of branded and generic drugs monitor the quality of materials across the entire supply chain and ultimately the APIs they use to produce their final drug products.

The benefits of an interoperable supply chain are extensive, and potential speed and efficiency gains across the value chain are tremendous, according to Valerie Van Hulle, global strategic marketing manager for digital at BASF.

“The process becomes much more efficient, fast, and with real-time data access,” agrees Selwyn Lustman, senior vice-president of global sourcing and procurement at LGM Pharma.

Instead of waiting for emails, phone calls, and even paper mail, companies can instantly exchange quality and regulatory content, supply-chain data, and other critical data. This ability leads to better collaboration between suppliers and manufacturers and, ultimately, improved assurance of API quality, Van Hulle explains.

For instance, says Lustman, pre-shipment certificate-of-analysis (CoA) approval carried out within a day and digitalized documents reaching the forwarder before goods arrive at port so preclearance of goods can be reached are just two examples of the faster flow of information made possible with digitalization.

In addition to enabling companies to collect and analyze data in real time, allowing for decisions to be made quickly, Lustman also says that digitalization can facilitate traceability and transparency. That is achieved, Van Hulle says, by sharing data via electronic data interchanges (EDI), application programming interfaces, and other software.

“The receiving organization can embed [these] data directly into their own systems, supporting their internal processes and opening the door to big-data analytics,” observes Van Hulle. “When it comes to quality,” she notes, “such advances can help companies maintain a much higher level of transparency, traceability, and accuracy throughout the manufacturing and supply chain process.” Companies are also recognizing that data sharing methods allow for greater flexibility, she adds.

Connecting data across the supply chain creates a single source of truth, Van Hulle asserts. “Connectivity requires a common language, and essential content such as terms and application programming interface metrics would be spoken in a single language, eliminating the need to compare ‘apples and oranges,’” she asserts. This consistency would drive further efficiencies and boost the quality of data across the value chain.

Still premature
API manufacturing digitalization is, however, still premature, and it is hard to say whether this process can fully be digitalized, according to Lina Cogan, senior director of global sourcing and procurement at LGM Pharma. Compared to other high-tech industries, the pharmaceutical industry has much work to do, Van Hulle agrees.

“While there are pockets of digital expertise (e.g., modeling, advanced analytics), digital solutions have not yet been broadly deployed,” says Van Hulle. Even leading API manufacturers

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still produce drug substances in a more “manual environment”, adds Cogan, with batch records handwritten most of the time and handled by operators on the spot who document each and every activity as required according to current good manufacturing practice (CGMP) regulations. “API manufacturers still work manually both in production and various labs and rely on their people to document each and every step to comply with GMP regulations and requirements,” she says.

Progress is being made
Van Hulle does note, however, that organizations and people are quickly realizing the benefits of digitalization and understand that customers, regulatory authorities, and partners are demanding a greater level of connectivity. As an example, she points to BASF’s exploration of the use of both virtual and remote audits of API and excipient manufacturing sites, which was enabled through digitalization, and an essential innovation during the COVID-19 pandemic to ensure high quality supply.

Many processes in the supply chain have been digitized over the past 10–15 years, Lustman adds. For instance, at LGM Pharma, purchase orders are sent digitally, and CoAs for pre-shipment approval are provided digitally, so clients can ensure that material meets their quality requirements before shipment. In addition, he notes that most shipping documents from contract manufacturers are sent digitally to clients, so they can be provided to forwarders and authorities for release of the goods from customs.

Another example of increasing importance for biologic drug substances and vaccines is the use of advanced digital trackers for cold-chain shipments, according to Lustman. The trackers provide downloadable data throughout shipment so drug manufacturers know their products are delivered in good conditions. In the past, data loggers had to be sent back to the manufacturer for downloading of the information, delaying the release of the API on the client side. The new technology allows more efficient release of goods via government agencies as well, he adds.

Several challenges
The fact that some suppliers and manufacturers have progressed with digitalization while others still operate manually makes sharing data across the pharma supply value chain difficult. “Some companies are leveraging cloud systems and have fully digitized their operations while others are still relying on paper records. It is extremely challenging to share data across systems that are not prepared to do so, let alone between different systems,” Van Hulle comments.

“If the pharmaceutical industry is to achieve real-time level data sharing, companies must first look at their end-to-end IT structures and ensure they are ready for an exchange,” Van Hulle asserts. Greater connectivity also requires the adoption of data-sharing standards. “Common standards could speed up the connectivity process and incentivize companies to invest in compatible electronic solutions,” she says. BASF is, for instance, exploring how ASTM and other existing standards can help make data sharing possible.

Some regulations may also need to change. One challenge to digitalization of supply-chain data that LGM Pharma has observed is the need for certain types of APIs, such as scheduled products, to have original documentation. “Original documents have to be sent from the client to the contract manufacturer, and only once government authorities approve them can shipments take place. This process can take several weeks,” Cogan explains.

Strategic approach needed
Digitalization should not be done for the sake of “going digital” but with a focus on addressing pain points, according to Van Hulle. “There is an abundance of new technologies available to support supply chain digitalization. Attempting to implement every digital solution can be overwhelming and lead to less-than-impactful investments,” she observes.

Organizations should look at how digital solutions can alleviate their supply-chain challenges and address evolving customer demands that can be met through digitalization. “Ultimately,” Van Hulle concludes, “digitalization of the supply chain is a great answer to many of these challenges and the first step in a company’s digital transformation.”

Two digitalization examples
Industry suppliers that have recently announced digital supply-chain solutions include PCI Services and MilliporeSigma.

The launch of its pci | bridge platform in the fall of 2020 was one of many initiatives that PCI has undertaken to incorporate digital transformation as core to its business strategy, according the company (1). The digital solution makes real-time information readily accessible to clients including inventory, production, distribution, and shipping data, presented in organized, customizable formats. The platform also features a document repository where electronic paperwork can be stored and accessed in one place and signatures secured on the platform.

MilliporeSigma’s eMERGE Program is a standardized platform solution for the exchange of data via an XML machine readable format based on an existing ASTM industry standard (ASTM E3077-17), including COAs and certificates of quality (2). It is compatible with existing process monitoring and analytics systems, enabling end users to integrate raw material data directly into their internal knowledge management systems and process analytical tools for improved monitoring and analysis of production performance, a better understanding of how raw materials impact processes and product variability, and a more efficient investigations process for out-of-specification situations.

References
Amorphous solid dispersions can overcome the pH effect encountered with oral oncology medications. ASDs can improve crystalline drug products in many ways, including by removing food–drug and drug–drug interactions (DDIs), decreasing dose, and reducing variability in plasma exposure (2). While these benefits can be realized across therapeutic areas, oncology is particularly relevant as it accounts for 25% of drugs approved by FDA in the last decade, and many oncology drugs are poorly water soluble across at least part of the GI pH range (3,4). Poor oral bioavailability in oncology is common, often manifesting as food–drug interactions, variation in exposure, and DDIs (5). Numerous marketed weak base, oral oncology drugs show decreased absorption as a result of high gastric pH when taken with acid reducing agents (ARAs) (6,7).

Calquence (crystalline acalabrutinib) is an example of a commercially marketed oncology drug that could benefit from bioavailability enhancement using ASDs (8). Acalabrutinib is a weak base with poor solubility at high gastric pH, resulting in clinically significant DDIs with ARAs. When administered with the proton pump inhibitor (PPI), omeprazole, the area under the plasma drug concentration–time curve (AUC) decreased by 43% in healthy volunteers (9). To prevent this issue, patients must avoid coadministration with PPIs and stagger dosing with histamine type 2 (H2) receptor antagonists (H2RAs) and antacids (9). Because ARAs are commonly taken by oncology patients, this DDI can reduce efficacy and patient compliance because of the complex dosing schedules required (10).

ASDs can improve outcomes for patients taking Calquence (acalabrutinib) by increasing acalabrutinib bioavailability at high gastric pH, thereby removing the DDI with ARAs. This article describes development of an ASD tablet that removed the acalabrutinib pH effect and outperformed Calquence 2.4-fold in the presence of the ARA, famotidine, at the human-prescribed (100 mg) dose in beagle dogs (11). ASD tablets were 60% smaller than Calquence and achieved good stability and manufacturability. These results have positive implications for using ASDs to solve bioavailability challenges, particularly for weak base drugs, which make up 78% of new molecular entities approved between 2003 and 2013 that showed clinical DDIs with ARAs (12).

ASD tablet development strategy
Designing tablets to overcome the Calquence ARA effect required an understanding of acalabrutinib’s physicochemical properties and the mechanism of reduced performance of crystalline acalabrutinib when taken with ARAs. Acalabrutinib is a Bioavailability Classification System (BCS) Class II drug with low intrinsic solubility and moderate log P (8). The drug is a weak base (pKa values = 3.5 and 5.8) causing it to become...
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ionized at low pH, resulting in moderately high solubility in the stomach of fasted humans (pH ~1–3) (13). However, as gastric pH increases with ARA administration (pH ~3–7) acalabrutinib is largely non-ionized and solubility is reduced, resulting in decreased dissolution, which decreases absorption across the intestinal membrane and increases the extent of dose metabolized in humans (8,14–17).

Therefore, an immediate-release ASD tablet was designed that maintained high dissolved acalabrutinib concentrations at both high and low gastric pH during in-vitro dissolution testing. In this case, high concentrations were defined as being at or above the value achieved with Calquence at low gastric pH (i.e., as prescribed). In addition, ASD tablets were designed to achieve good physical and chemical stability, good manufacturability, and to minimize size.

**ASD tablet manufacturing and characterization**

ASDs contain amorphous drug molecularly dispersed in a polymer matrix, which is used to stabilize the amorphous form during storage and in GI fluids (18). The acalabrutinib ASD consisted of 50/50 (% w/w) hydroxypropyl methylcellulose phthalate (HPMCP) as a polymer with sucrose palmitate and polysorbate 80 as surfactants in a hot-melt extrusion process.

In the study, Andreas Schittny et al. employed a model ASD formulation of efavirenz, which is an antiretroviral medication that is classified on the biopharmaceutics classification system as a class II drug—one with poor solubility but high permeability. The model formulation comprised hydroxypropyl methylcellulose phthalate (HPMCP) as a polymer with sucrose palmitate and polysorbate 80 as surfactants in a hot-melt extrusion process.

Sixteen healthy male patients were included in the study and were randomized to receive efavirenz in three different ways: intervention 1 was ASD of efavirenz (50 mg) as a capsule with 500 mL buffer solution; intervention 2 was dissolved ASD of efavirenz (50 mg) in 500 mL of buffer solution, forming drug-rich particles; and intervention 3 was efavirenz (3 mg) solution in a 500 mL buffer solution. The study participants were randomly selected to receive the interventions in different orders (either 1-2-3, 2-3-1, or 3-2-1) and a washout period of 14 to 21 days was performed between interventions.

Blood samples were obtained pre-dose and at multiple time points post-dose so that the plasma concentration of efavirenz could be determined through bioanalysis techniques. The pharmacokinetic profiles of efavirenz plasma concentrations compared to time were used as the primary study endpoints, with further pharmacokinetic analysis and modeling used as secondary endpoints. Furthermore, study results were compared with existing pharmacokinetic data available for a marketed formulation of efavirenz (Stocrin).

Based on the study results, it was found that the dissolved ASD of 50 mg of efavirenz (intervention 2) pharmacokinetically behaved nearly identically to the solution of efavirenz 3 mg (intervention 3). Therefore, intervention 2, which comprised a supersaturated aqueous solution containing drug-rich particles, behaved as a solution, and assuming passive absorption, the researchers deduced that the dissolved drug concentration in the intestine of intervention 3 was higher by a factor of 16.7 than intervention 2.

As a result of the drug concentration exceeding that of the aqueous solubility of efavirenz, it was concluded that drug-rich particles from ASDs are efficient oral drug delivery systems and drug absorption was fast and complete in humans. Additionally, the findings of the study confirmed the conceptual models of how drug molecules are released from ASDs and how they are subsequently absorbed into the intestinal tract.

**Recent Research on Amorphous Solid Dispersions**

**Insights into underlying mechanisms of ASDs**

Researchers from the University of Basel in Switzerland and The Peoples’ Friendship University of Russia (RUDN University), investigated the underlying drug absorption mechanisms of amorphous solid dispersions (ASDs), proving the effectiveness of a novel, particle-forming ASD drug-delivery system for poorly soluble compounds (1).

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Acalabrutinib/hydroxypropyl methylcellulose acetate succinate (HPMCAS-H) (Aqoat, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan). HPMCAS is an ideal polymer for ASDs as a result of its high glass transition temperature and low hygroscopicity, facilitating high ASD physical stability during storage, and its amphiphilicity, promoting favorable interactions with hydrophobic drugs and intestinal fluids to inhibit crystallization in the GI tract (11,19).

The ASD was manufactured in a customized, laboratory-scale spray dryer and secondary dried in a vacuum dryer with high yield (97%) and low residual spray solvent (100 ppm methanol). In the spray drying process, drug and polymer are dissolved in an organic solvent and sprayed through an atomizer nozzle to create small droplets. At the same time, a drying gas is pumped into the spray dryer to rapidly evaporate solvent and lock the drug and polymer into a homogeneous amorphous solid dispersion. The resulting ASD particles are separated from the gas stream and collected for processing into a final dosage form (20). Spray drying is a scalable process precedent in commercial manufacturing of ASDs (21).

ASD was confirmed to be amorphous and homogenous using powder X-ray diffraction (PXRD) and modulated differential scanning calorimetry (mDSC), with a lack of surface crystals using scanning electron microscopy (SEM) (11). In addition, the ASD was confirmed to remain amorphous and homogenous after open storage for six months at accelerated temperature and relative humidity (40 °C/75% RH) as measured by PXRD, mDSC, and SEM, indicating good ASD physical stability and a good outlook for storage at ambient or refrigerated conditions over a typical product shelf life (i.e., two years) (11).

ASD was dry granulated with excipients and compressed into tablets using a small-scale manufacturing process. ASD tablets had a 100-mg unit dosage strength, a 25 wt% drug loading, and a 60% smaller volume than Calquence capsules (11). ASD tablets were found to be chemically stable when stored at room temperature with desiccant or in the refrigerator, which are acceptable storage conditions for pharmaceutical drug products (11).

![Figure 1: Acalabrutinib concentration time profiles in the in-vitro controlled transfer dissolution (CTD) test for amorphous solid dispersion (ASD) tablet and commercial Calquence capsule at gastric pH 2, 'without acid reducing agent (ARA)' (top) and gastric pH 6, 'with ARA' (bottom) (11).](image1)

![Figure 2: Acalabrutinib plasma concentration time profiles in fasted beagle dogs for amorphous solid dispersion (ASD) tablets and commercial Calquence capsules at low gastric pH (without acid reducing agent [ARA], treated with 6 mg/kg subcutaneous pentagastrin) and high gastric pH (with ARA, treated with 40 mg oral famotidine) (7 day washout between phases, n=6) (11).](image2)
### Table I. Acalabrutinib under the plasma drug concentration–time curve (AUC) from time zero extrapolated to infinity for amorphous solid dispersion (ASD) tablets and commercial Calquence capsules at low gastric pH (without acid reducing agent [ARA], treated with 6 mg/kg subcutaneous pentagastrin) and high gastric pH (with ARA, treated with 40 mg oral famotidine) (7 day washout between phases, n=6) (11).  

<table>
<thead>
<tr>
<th>Article, treatment</th>
<th>ASD tablet, low pH</th>
<th>ASD tablet, high pH (ARA)</th>
<th>CalQUENCE capsule, low pH</th>
<th>CalQUENCE capsule, high pH (ARA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng·h/mL)</td>
<td>8161 (1364)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7579 (1423)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8365 (1201)</td>
<td>3112 (1415)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>AUC compared to CalQUENCE capsule, pentagastrin</td>
<td>0.98</td>
<td>0.91</td>
<td>1</td>
<td>0.37</td>
</tr>
</tbody>
</table>

<sup>a</sup> Statistically equivalent to CalQUENCE capsule, pentagastrin (p > 0.05).  
<sup>b</sup> Statistically different from CalQUENCE capsule, pentagastrin (p < 0.05).

### ASD tablet in-vitro performance

Effective development of ASD dosage forms requires use of biopredictive in-vitro dissolution methods to evaluate drug formulation performance under varying GI conditions (22). In this study a custom, controlled-transfer dissolution (CTD) apparatus containing simulated gastric and intestinal compartments was selected to study dissolution performance of the ASD tablet and commercial Calquence capsule (11,23). Testing was conducted prior to the in-vivo study in conditions representative of fasted beagle dogs treated with either pentagastrin or famotidine to lower or raise gastric pH, respectively. Simulated gastric fluid comprised hydrochloric acid adjusted to pH 2 or 6, and simulated intestinal fluid consisted of pH 6.5 phosphate buffer containing bile salts and phospholipids (i.e., FaSSIF powder, Biorelevant.com Ltd. [London, UK]) at levels characteristic of fasted beagle dogs (average of 6.7 mM) (11). Dosage forms were added to the gastric compartment of the CTD, and fiber-optic ultraviolet probes were used to monitor acalabrutinib concentrations in the gastric and intestinal compartments with time as gastric contents transited to the intestinal compartment at a physiological gastric emptying rate (15-min mono-exponential half-life).

As shown in Figure 1, the ASD tablet and Calquence capsule achieved similar concentration–time profiles at low gastric pH (pH = 2) due to the high solubility of both crystalline and amorphous acalabrutinib. Both dosage forms reached high drug concentrations in the gastric compartment and supersaturated in the intestinal compartment for the duration of the experiment. However, at elevated gastric pH simulating fasted beagle dogs taking an ARA (pH = 6), the ASD tablet outperformed Calquence due to the higher solubility of amorphous acalabrutinib. At elevated gastric pH the ASD tablet reached higher maximum concentrations and a 3.4-fold higher average AUC in the intestinal compartment than CalQUENCE. Whereas the ASD tablet achieved supersaturated drug concentrations in both compartments, the CalQUENCE capsule was solubility-limited and did not achieve supersaturated drug concentrations. The ASD tablet mitigated the ARA effect in vitro, where average AUC in the intestinal compartment at elevated gastric pH is 83% of that at low gastric pH.

### ASD tablet in-vivo performance

Beagle dogs are a commonly used species for testing dosage form performance prior to clinical testing in humans. To demonstrate mitigation of the CalQUENCE ARA effect in vivo, ASD tablets and commercial CalQUENCE capsules were administered to beagle dogs in a crossover study at the human prescribed 100-mg dose in compliance with the Animal Welfare Act Regulations (9 Code of Federal Regulation 3). To study performance in the absence of an ARA, six dogs were given a subcutaneous injection of pentagastrin to lower gastric pH; whereas to determine performance in the presence of an ARA, the same dogs were treated with oral famotidine to increase gastric pH (24,25). Blood was collected for up to 24 hours after dosing, and acalabrutinib plasma concentrations were determined by liquid chromatography–tandem mass spectrometry (11).

As shown in Figure 2 and Table I, ASD tablets achieved similar concentration–time profiles and AUC at low and high gastric pH conditions and matched performance of CalQUENCE at low gastric pH conditions. Whereas, CalQUENCE capsules demonstrated an ARA effect, achieving only 37% of the average AUC achieved at low gastric pH conditions. At high gastric pH conditions, ASD tablets outperformed CalQUENCE capsules, with a 2.4-fold higher average AUC. These results show that ASD tablets overcame the ARA effect and achieved performance (e.g., average AUC) of CalQUENCE as prescribed (11). Furthermore, in-vitro results were in line with in-vitro dissolution testing in the CTD apparatus, which predicted similar performance of the ASD tablet and CalQUENCE at low gastric pH, ability of the ASD tablet to mitigate the ARA effect, and superior performance of the ASD tablet to the CalQUENCE capsule at high gastric pH.

### Conclusion

ASD tablets were shown to overcome the ARA (i.e., pH) effect observed with the oral oncology medication, CalQUENCE, at a 60% smaller dosage unit size in fasted beagle dogs. Whereas ASD tablets achieved similar average AUC in dogs under low and high gastric pH conditions, CalQUENCE capsules achieved a 63% lower,
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Implementing Data Integrity Compliance in a GLP Test Facility

Simone Cossari, Erica Aloisio, Valerio Capirone, Raffaele Lasala, and Stefano Simonato

Consider how to apply ALCOA+ to a building management system in non-clinical laboratories.

GLPs and data integrity
GLPs, as described by the Organization for the Economic Cooperation and Development (OECD), “promote the quality and validity of test data used for determining the safety of chemicals and chemicals products” (1) and promote the mutual acceptance of these data be-

between the OECD member states. GLP principles “are required to be followed by test facilities carrying out studies to be submitted to national authorities for the purposes of assessment of chemicals and other uses relating to the protection of man and the environment” (1).

The GLP principles should be applied to the management and handling of test items investigated in the context of pre-clinical safety studies. Because GLP covers processes leading to the release of data, data integrity principles must be followed, as is discussed in OECD Series #1 (1).

OECD Series #1 was initially addressed to a set of data mainly generated and recorded on paper and magnetic support; thus, the definition of data (“Raw Data”) was general and “in principle”. The increase of data sets generated and recorded by computerized systems and automatized solutions, however, led to the need to cover new definitions and management of data for topics such as computerized system validation, e-archives, electronic records, and electronic signatures. These topics were addressed in United States 21 Code of Federal Regulations Part 11 (2), OECD GLP Series #15 (3), and OECD GLP Series #17 (4), which have become reference documents for the pharmaceutical industry regarding data integrity (see Figure 1 for a timeline).

OECD GLP Series #17 gives the proper definition of data (raw data), defined as “a measurable or descriptive attribute of a physical entity, process or event. The GLP principles define raw data as all laboratory records and documentation, including data directly entered into a computer through an automatic instrument interface, which are the results of primary observations and activities in a study and which are necessary for the reconstruction and evaluation of the report of that study” (4).

OECD is working on a draft guidance document on data integrity to make data integrity concepts more explicit and clarify issues already faced by earlier monographs (e.g., #15 and #17). This new guidance aims “to promote a risk-based approach to the management of data, which includes data risk, criticality, and lifecycle” (5), based on the key concepts contained in the ALCOA+ acronym, in which data in GLP studies should be:

- Attributable (to the person and system generating data)
- Legible and permanent
- Contemporaneous
- Original record (or certified true copy)
- Accurate
- + (complete, consistent, enduring, available).

Case study: building management system
Building management systems (BMSs) are automation systems for controlling and monitoring buildings, premises, and facilities related to fire detection, anti-intrusion, access control, ventilation, equipment (e.g., refrigerator, and incubator probes), and environmental conditions (e.g., temperature, humidity, pressure, and air changes). The BMS system can be considered to
cover in its scope the first three levels of the ISA-95 automation pyramid (6). In Level 0, which is the field level (e.g., sensors, probes, actuators), the BMS captures any signals from the field, sending them to the control level, or the BMS actuates any signals coming from the control level. Level 1, the control level, contains programmable logic controllers (PLCs), which are formed by a central unit, input/output units, and a programmable unit. The PLC functions to execute the program by elaborating outputs (e.g., acting on valves) according to received inputs (e.g., temperature sensors). Level 2 is the supervisory level, with a human-machine interface. The supervisory level is based on client-server model: a main server collects data from PLCs and stores them in a database, while a web server hosts BMS web application that connects to the database and satisfies client requests. Users get access to the system from several devices (e.g., office laptops, tablets, and dedicated desktop workstations located in the labs) using a web browser; they can change settings on PLCs (e.g., setpoints) and monitor data coming from field devices. These levels communicate with each other by using predefined protocols.

The major advantages of using a web-based application, illustrated in Figure 2, are:

- Minimal information technology department (IT) maintenance effort. IT will only have to ensure compatibility between the web browser and the BMS web application. Installation and upgrade of any software on client computers are avoided.
- Personnel save time accessing the BMS from personal computers in the office or from home, connected to the company network. If a computer is stolen or damaged, data are not at risk because they are stored in the BMS database.
- PLC maintenance is simplified using web-based diagnostics.

**Data integrity compliance**

The BMS’s functionalities make it suitable for the pharmaceutical industry to monitor the storage and environmental conditions of test items, test reference items, test systems, and specimens generated by the study conduct, as well as avoiding uncontrolled access to the facilities. The BMS manages critical records, which are the object of health authorities’ study-related inspections. These data (metadata and raw data) that are part of the critical records include:

- Regulated data automatically captured from qualified instruments (equipment and environmental conditions, and access control)
- Study personnel manual data entries
- Data trends (e.g., temperature, carbon dioxide concentration, relative humidity, pressure, air changes)
- Alarms and events related to critical data
- Reports
- Audit trails.

How can these critical records be made compliant with regulatory requirements? To answer this question, it can be helpful to introduce the concept of data governance, described as “the sum total of arrangements to ensure that data are complete, consistent, and accurate throughout their lifecycle” (5).

Data governance control strategies should be implemented to achieve data integrity. According to a World Health Organization draft guideline (7), controls may be:

- Technical (system functionalities and configurations)
- Procedural (GLP process-based procedures implementations)
- Organizational and behavioral (quality and data integrity culture promoted by test facility management).

When implementing the BMS in a lab, the authors used the following best practices to reflect ALCOA+ principles.

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**Figure 1.** A timeline of good laboratory practice (GLP) guidances from FDA, Organization for the Economic Cooperation and Development (OECD), the International Society for Pharmaceutical Engineering (ISPE) good automation manufacturing practice (GAMP), and the United Kingdom’s Medicines and Healthcare products Regulatory Agency (MHRA). GxP is an abbreviation for good practices.
Attributable (A). This principle requires that data are attributed to the person or system that generates or modifies data, and that the data are attributable to the study.

The technical implications are that the following should be set up in the BMS:
- Access control configuration (individual identification and password)
- Roles and permission configuration according to job title
- Audit trail configuration: data and actions attributable to a specific individual
- Audit trail: users management
- Report configuration: attributable to the person generating it
- Data trends configuration: trends attributable to specific equipment
- Filtering records according to the period when the study has been conducted.

BMS management procedures should include:
- Authorization process flow to use the system approved by test facility management
- Audit trail (periodic and for critical changes) reviews.

Legible and permanent (L). This principle requires that data are readable throughout the data lifecycle.

The technical implications are that the following should be set up in the BMS:
- System generating human readable records
- System generating accurate and complete copies of records in other formats
- Configuration of automatic reports generation
- Audit trail available and convertible in a human readable format
- Data not overwritable
- Audit trail tracing old/new values
- Easily visible critical parameters via graphical configuration.

Contemporaneous (C). The expectation is that data are recorded when the work is performed.

The technical implications are that the following should be set up in the BMS:
- System clock (date, time, and time zone) locked by any possible change
- Clock synchronization with Network Time Protocol qualified server
- Audit trail recording correct time stamps
- Time stamped reports.

Original (O). Original data are the first capture of information or a certified ‘true copy’.

The technical implications are that the following should be set up in the BMS:
- Raw data and metadata not overwritable
- Data folder configuration: not disposable records
- Automatic database backup
- Server snapshot.

Procedures should cover:
- Identification of critical records based on risk approach and data process flow definition
- Backup and restore service level agreement with IT function and supplier
- Disaster recovery.

Accurate (A). Accuracy requires that records are error-free and that any edits are documented.

The technical implications are that the following should be set up in the BMS:
- Complete audit trail configuration (who, when, why, what)
- Field level equipment calibration
- Infrastructure qualification.

BMS management procedure should include:
- System validation
- Audit trail (periodic and for critical changes) reviews.

Plus (+). These principles require the presence of a complete set of data (including relevant metadata) and that data must be self-consistent (e.g., through the application of good documentation practices); are kept in a durable, permanent, maintainable form throughout the entire data life cycle; and are available and accessible for review or inspection purposes throughout the retention period. GLP archive process compliance (e.g., long term availability and readability of records) is required.

The technical implications are that the following should be set up in the BMS:
- Automatized data archive
- Qualified archive server.

BMS management procedure should include:
- System periodic review
- Data retention and archive standard operating procedures (SOPs).
Meeting Development and Manufacturing Demands for Emerging Therapies

Event Overview
Cell therapies and gene therapies continue to challenge the development and manufacturing capabilities of biopharma companies and contract manufacturers. These therapies and personalized medicines, however, require analytical methods, supply chains, manufacturing processes, and regulatory standards that may be different from more traditional biologic drug development and manufacturing.

This Technology Forum will explore the current state of commercialization for cell and gene therapies and the patient and physician perspective, as well as the need for technologies, processes, and strategies to ensure competent delivery of these treatments to patients.

Among the challenges to be addressed are capacity scale up, material shortages, and temperature-dependent requirements as well as the variables (e.g., type of diseases, patient health conditions, strict time constraints, etc.) that drive turnaround times for cell and gene therapies, and, therefore, the need for innovative production, logistics, and delivery technologies.

Key Learning Objectives
Topics discussed during this webcast include the following:

- Review current market and regulatory dynamics for cell and gene therapies.
- Understand the development and manufacturing challenges from the patient perspective.
- Learn about technologies and processes to facilitate development and manufacturing.
- Hear about efforts to reduce turnaround time, ensure a safe supply chain, and manage delivery to patients.

Who Should Watch
- Small biotech companies developing cell therapies and gene therapies
- Development and manufacturing teams at mid-size and large bio/pharma companies
- Corporate and development experts
- Process development and manufacturing experts

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www.pharmtech.com/pt_p/interphex3

For questions email kbarry@mjlifesciences.com
For all ALCOA+ requirements, behavioral implications include the following:

- Test facility management (TFM) promoting quality culture based on data integrity
- TFM promoting investigation and analysis
- TFM enabling visibility of errors and misconduct
- TFM ensuring appropriate resources to ensure data governance
- Quality assurance unit conducting audits to determine GLP and data integrity compliance
- Study personnel trained on data integrity principles
- Study personnel trained on system-specific SOPs
- TFM promoting risk-based approach
- Site data integrity maturity level. It is clear that system functionalities and technical and procedural implement-ations are crucial and represent key tools to achieve data integrity, but they are not enough. Because process knowledge and human factors play important roles within data governance, behavioral implications must also be considered. A risk-based approach to the system and process in scope is of paramount importance to harmonize the GLP requirements with the technical resources and constraints as well. This approach results in a dynamic relationship between the technical solutions of the system and the satisfaction of the regulation provisions and requirements. Because this relationship is dynamic, close collaboration of several functions is needed; the quality assurance unit, test facility management, study directors, and technical experts configuring the system and performing the activities on it must continuously interact to sustain compliance.

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Dry Powder Inhalation Delivery of Monoclonal Antibodies

ON-DEMAND WEBCAST
Aired: Thursday, July 22, 2021

Presenter
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Moderator
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Event Overview
Monoclonal antibodies (mAbs) are powerful therapeutics that address unmet treatment needs in a wide range of serious diseases. Local delivery of mAbs used in treatment of lung indications via the inhalation route may help reduce dose, limit systemic exposure of healthy tissues, and lessen adverse events, while improving patient compliance and lowering cost of treatment.

This webinar describes the use of spray drying to manufacture dry-powder inhaled formulations of a monoclonal antibody for lung cancer. The resulting formulation was shown to be shelf-stable at ambient temperature, have aerosol properties targeted for delivery to the deep lung, and was efficacious at reducing tumor burden in a rat model of non-small-cell lung cancer.

Key Learning Objectives
• Understand the therapeutic value of pulmonary delivery for lung indications
• Learn how spray drying can be used to manufacture dry-powder inhalation formulations of monoclonal antibodies
• Recognize the challenges associated with spray drying of biotherapeutics for inhalation delivery

Who Should Watch
• Decision-makers at biopharma companies
• Pharmaceutical scientists and formulators
• Engineers working in pharmaceutical manufacturing
• Students interested in the pharma industry

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Register for this free webcast at:
www.pharmtech.com/pt_p/powder
that will be injected into a human patient. Particulate contamination needs to be carefully controlled in the cleanroom by filtration and air exchange. Different types of cleanrooms control airborne particulates to different levels. Inside the cleanroom itself, manual and automated methods are used for the disinfection of surfaces and equipment, but such practices can damage equipment materials and electronics. To minimize damage, laboratory equipment should be tested to demonstrate compatibility with chemicals and application methods.

Regulatory audits help ensure the safety, efficacy, purity, and quality of a product by reviewing documentation that accompanies every step of the process. A CO₂ incubator supported with a comprehensive documentation package will help ease the path to regulatory approval.

**Optimizing growth conditions**

In the production of cells for human therapy, CO₂ incubators must provide a highly controlled environment to support optimal cell growth, ensuring proper gene expression, limiting stress responses, and preserving characteristics critical to the success of the therapy. Equipment design and engineering play a critical role in how cells grow; different incubator models show widely different performance (3), even if functional specifications are similar. Ideally, CO₂ incubators used in cell production should offer recovery of all conditions (i.e., temperature, CO₂ gas concentration, and humidity) in 10 minutes or less following a 30-second door opening. Fast recovery ensures sensitive stem and primary cells remain in their ideal growth environment (see Table I for the maximum time during production, helping to ensure high-quality cell therapy products.

One technical aspect involved in the recovery of parameters is the quality and location of sensors. Sensors used to measure temperature, gas concentration, and relative humidity should be located inside the chamber where the cells are incubated, rather than using a bypass sensor located in a separate electronics compartment (4). In-chamber sensors
are positioned to measure and react to the same conditions experienced by the cultured cells.

Another design element critical to parameter recovery and uniformity of conditions in the incubator chamber is active air circulation. Warm air rises, and CO₂ gas sinks because it is heavier than air. Without active air circulation, atmospheric conditions will stratify, meaning cultures in different areas of the incubator experience different conditions. To ensure the consistent growth of all cultures, a circulating fan is required.

Sterilization and filtration
Microbial contamination is a significant concern for cell therapy, with mycoplasma species discovered in 15–35% of all cell cultures in 2015 (5). Different approaches to contamination control can be used, but the best way to select such a method is to look for proof of efficacy. For example, a dry heat sterilization cycle built into a CO₂ incubator should be proven according to the precepts in the pharmacopeias from the United States (6) and the European Union (7). Both require proof of elimination of one million specific, heat-resistant bacterial endospores. The US Pharmacopeia additionally requires an “over-kill” approach for a total 12-log sterility assurance level (SAL). Both pharmacopeias require hot air to be continuously circulated using a fan. To ensure no cold spots where microorganism could survive, the entire incubation chamber should be mapped to confirm that all areas reach the specified temperature.

A 12-log SAL sterilization is effective at eliminating microorganisms in the chamber, but an in-chamber high-efficiency particulate air (HEPA) filtration system provides 24/7 protection from airborne microorganisms. This filtration is important because each time the incubator door is opened, surrounding air can enter the incubator interior, including circulating microbes. Recovery time of the incubator to cleanroom conditions is an important parameter to consider. For example, in a Thermo Scientific incubator design, an H13-rated HEPA filter combined with active airflow captures all microorganisms regardless of size, providing ISO Class 5 cleanroom conditions in five minutes following a 30-second door opening. This design filters the entire chamber air volume every 60 seconds, approaching zero particulates circulating over time. The filters are rated for one year of average use.

Removing the risk of non-viable particles
The dangers posed by microscopic particles are not limited to microorganisms. Non-viable particles from personnel, equipment, and consumables also carry safety and efficacy risks: 22% of FDA recalls of sterile injectables between 2008 and 2012 were due to non-viable particulates (8), representing the second leading cause of recalls between 2009 to 2019 (9). Personnel regularly monitor particulate counts in a cleanroom to ensure compliance. The most common particulates are bits of metal, glass, plastic, hair, rubber, cell debris, and fabric (10).

While approximately 70% of non-viable particulates come from personnel in the cleanroom, about 15% come from the equipment (10) used to grow and process the cultures. With this in mind, equipment manufacturers are starting to consider how their designs can better complement a cleanroom setting and limit the number of particulates released. A cleanroom-certified design is carefully tested by a qualified industry institute with clearly documented procedures, such as those outlined in ISO 14644-14 (11).

In a design used in cleanroom-certified incubators from Thermo Fisher Scientific, for example, a HEPA filtration system limits particulate release to the cleanroom. The entire external casing is sealed, and a vacuum system captures particulates, passing them to the HEPA filter at the rear (see Figure 1). Incoming air to cool the electronics is also filtered.

Withstanding cleaning and disinfection
It is impossible to test all chemical disinfectants available globally, but some common usage exists. For example, hydrogen peroxide is a broad-spectrum disinfectant and, in low concentrations of 1–6%, it is generally compatible with paint, stainless steel, glass, and plastics. For any chemical disinfectant, it is important to follow the manufacturer’s recommendations for dwell time, recommended dilution, and personnel protection. It is best practice to follow any aggressive disinfectant, including hydrogen peroxide, with a 70% ethanol (EtOH) or 70% isopropanol (IPA) solution to remove any residues and protect from chemical buildup that, over time, could degrade equipment materials. It is particularly important to remove strong chemical residues from a cell culture incubator to limit fumes that could harm cultured cells and elicit stress responses (12,13).

Another approach common to cleanroom sterilization is fumigation using
vaporized hydrogen peroxide (VHP). Depending on the provider, VHP can include a range of hydrogen peroxide concentrations and added chemicals such as peracetic acid. Condensation of high concentration VHP chemicals can damage incubator materials over time and can cause peeling of painted steel surfaces. For these reasons, any VHP process should carefully control condensation—commonly referred to as a ‘dry process’—and provide proof of sterilization and neutralization of the chemicals to prevent potential harm to equipment, cultured cells, and personnel.

For increased compatibility with chemical disinfectants and VHP, a brushed 304 stainless-steel exterior is recommended. Ingress protection 54 (IP54)-rated electronics and a silicone-sealed touchscreen display increase compatibility with such processes, protecting from dirt and splashed liquids. An electropolished stainless-steel incubator chamber and components mean reduced microscopic structures for easier cleaning and limited areas for microorganism attachment.

**Documentation for cleanroom compliance**

To ease equipment qualification and help meet audit requirements, full factory acceptance testing (FAT) and applicable certificates and sourcing documentation are essential. Such documentation should be provided by the CO₂ incubator manufacturer and include:

- Technical specifications
- Equipment drawings
- Preventive maintenance checklists and evidence
- Replaceable parts list and dates of last replacement
- EC, UL, REACH, and ISO 13485 certificates
- Material certification
- Certificates of quality
- FAT reports
- Sensor certifications
- Accessory validation protocols.

**Supporting the growing cell therapy market**

CO₂ incubators are critical for the creation and maintenance of optimal cell growth conditions, encouraging the cellular responses seen in vivo that are necessary for cell therapy success. A cleanroom-compliant CO₂ incubator is certified to control particulate emission, withstand stringent cleaning protocols, and provide conditions for sensitive cells to promote their consistent growth and expression.

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ON-DEMAND WEBCAST
Aired: Thursday, August 5, 2021

**Presenter**

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**Moderator**

Rita Peters  
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**Event Overview**

This seminar will provide an overview of the regulatory framework that generic ophthalmic drug products are subject to, and approved under, as well as discuss the current thinking and scientific challenges with studies that may be recommended to demonstrate bioequivalence (BE). Of the more than 150 approved brand-name ophthalmology products that can serve as a reference listed drug (RLD), less than half currently have an approved generic product. In particular, the development and approval of complex generic ophthalmic formulations such as emulsions, suspensions, gels, ointments and implants can be challenging. To help address these challenges and facilitate complex generic drug development and regulatory assessment, FDA oversees a Generic Drug User Fee Amendments (GDUFA) research program. Highlights of recent GDUFA-funded ophthalmic research projects will be discussed. This will include research on new analytical testing methods (e.g., particle sizing and in vitro drug release methods) to assess more precisely the critical quality attributes (CQAs) and performance of complex ophthalmic formulations. In addition, recent pharmacokinetic and pharmacodynamic studies to better understand the in vivo impact of differences in product formulation and CQAs will be covered along with recent advances in the development of ocular physiologically-based pharmacokinetic (PBPK) modeling and simulation that can be used to support equivalence assessment standards for in vitro-based BE approaches.

**Key Learning Objectives**

- Understand the regulatory framework for generic ophthalmic drug products
- Hear about recent pharmacokinetic and pharmacodynamic studies to better understand the in-vivo impact of differences in product formulation
- Learn about recent advances in the development of ocular physiologically-based pharmacokinetic (PBPK) modeling and simulation

**Who Should Watch**

- Drug development scientists
- Generic drug manufacturers

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Serialization: Reducing Counterfeit Drugs and Increasing Sales

Scott Deakins

An effective data structure and simple communication between production, logistics, and sales is essential for delivering this level of accountability, traceability, and security.

The growth in counterfeit prescription medications—an estimated $200 billion in revenue, according to an October 2020 report by Statista—has become more pronounced (1). That’s $200 billion lost by bio/pharmaceutical companies and, as a result, Statista notes that the financial burden may prevent 13 new drugs from coming to market every single year (1).

While stringent about monitoring for counterfeit prescription medications, the United States is not spared. According to the National Crime Prevention Council, counterfeit pharmaceuticals account for more than 10% of all pharmaceuticals in the global supply chain (2). It may have once appeared to be a drop in the bucket for this global trillion-dollar industry, but fake pharmaceuticals continue to rise and threaten trust in the sector and present serious health implications for consumers.

For example, in December 2020, Janssen reported that a counterfeit version of its antiretroviral treatment for HIV-1, SYMTUZA, was circulating in the market. To combat this problem, the company said that it was developing special packaging and printing techniques to make counterfeit products easier to identify (3).

However, combatting counterfeit drugs is not a challenge any one company can solve. The key to protecting drug safety and consumer confidence is traceability down to the smallest packaging unit. Although federal and state laws apply stringent and coordinated restrictions on domestic supply, the absence of full unit-level traceability handicaps consumer protection and threatens the intellectual property of manufacturers.

The US Drug Supply Chain Security Act (DSCSA), passed by Congress in 2015 and scheduled for full enforcement in 2023, mandates that manufacturers assign unique codes to medicinal products that can be clearly traced from manufacturer to patient. For an industry with complex supply chains, this sweeping regulation presents challenges, including possible penalties for non-compliance and loss of efficiency. Manufacturers must consider a number of factors before DSCSA comes into full force.

Drug-makers must, therefore, serialize finished drug products down to the package level by 2023. They need to store all data associated with that finished product, including the unique product identifier, lot or batch number, and expiration date securely for extended periods of time, and be able to access it as required along the supply chain. In addition, transaction information and transaction statements must be exchanged by trading partners and maintained by the manufacturer.

An effective data structure and simple communication between production, logistics, and sales is essential for delivering this level of accountability, traceability, and security. Bio/pharmaceutical companies need to navigate this complexity to comply with regulations; however, there are technology tools to help create value for the company at the same time.

Enterprise resource planning to simplify serialization

ISA95, an international standard for developing an automated interface between enterprise and control systems from the International Society of Automation (ISA), identifies five levels of track, trace, and serialization technology. The goal of the standard is to reduce the risk, cost, and errors associated with implementing these interfaces.

The following describes the five levels of track-and-trace serialization.
and its integration with the production process:

- Level 0. Production process: Serialization numbers printed and inspected
- Level 1. Sensing/device controller: Serialization and aggregation data management per station
- Level 2. Line management: Serialization and aggregation data management for the entire packaging line
- Level 3. Manufacturing operations: Serialization and aggregation data management for the entire facility
- Level 4. Business planning: Serialization interface to enterprise resources planning (ERP) and manufacturing execution system
- Level 5. Global serialization and tracking

The relationship and communication standards between these levels may vary depending on the solution and the provider, which can lead to expensive mistakes when implementing serialization solutions.

A modern ERP that covers and supports all five levels of the serialization process can ease implementation by making the experience straightforward for users at multiple levels of the business. A solution that also controls general business processes can bolster the organization’s ability to comply by ensuring consistent quality throughout the supply chain and the production status can be traced to a batch or the smallest production unit. Serialization can also be used for aggregation to create child-to-parent relationships between individual units and the bundle, case, or pallet they came from for enhanced traceability.

Of the five levels of serialization, Levels 1-3 concern the local production facility. Here, the serialization codes are created and managed by the ERP, which assigns them to the units according to the manufacturing process, reducing manual implementation or stopgaps that may delay operations. Validation is creating scalable and repeatable business processes through an electronic system that provides checkpoints, electronic signatures, and an audit trail of all actions that have been completed. This validation is important in highly regulated industries such as pharmaceuticals. Companies need to prove to regulators, like the FDA, that they consistently follow the specific guidelines and regulations. A complex validation process can be facilitated by an ERP system with functions integrated in a single software system.

To maintain production speeds of more than 100 units per minute, the ERP system must be able to send codes to the packaging machine (Level 1), apply them, and directly compare them as quickly in parallel without interrupting or influencing the production speed. The ERP should automatically note and delete or release the corresponding serial numbers for and discarded individual units to errors with minimal manual intervention. The data from all packaging machines are aggregated on Level 2, while master data and serialization data are coordinated here at Level 3. Level 4 is integrated within enterprise resource planning systems to effectively track and trace all materials within the system at the local level. Last, Level 5 empowers drug-makers with global tracking to reach every supplier within its supply chain. Collectively, all levels of serialization are beneficial in the event of a recall.

The interaction of the software within the five levels reduces the burden of implementing serialization, improves production, saves intermediate steps, and enables company-wide reporting in real time. Some ERPs automatically create the necessary labels and documents required at each level, which allows manufacturers to pass products to customers for order processing immediately after they have been palletized.

**Line, operations, and supply chain in a single view**

The networking inside and outside the company takes place on Level 4 and Level 5 of ISA95. Serialization data must be communicated and administrated globally across manufacturers, service providers, customers, and government institutions. Coordinating all elements of the network streamlines business processes and compliance and brings complaints and reporting in the same view.

Instead of wondering where a particular ingredient has come from without any way of definitively determining its source, streamlining serialization data allows bio/pharmaceutical companies to guard the supply chain against counterfeit drugs. This is important because, without the ability to meticulously drill down and uncover where a crate or pallet is or where the contents have come from, bio/pharmaceutical manufacturers—and ultimately the supply chain—would remain vulnerable. They may unknowingly deploy counterfeit components thinking they came from legitimate sources. But they cannot rely on thinking alone; they must know the source of everything that goes into their prescription drugs. That is only possible by streamlining serialization data.

But the streamlining of serialization data can be used for more than guarding the supply chain against counterfeit drugs. By optimizing data from the five levels of serialization in a single software system, decision makers can gain insights across the supply chain to analyze product flows, understand logistics, transport processes, and make the changes to remove inefficiencies. Siloed data is one such inefficiency, as pharmaceutical companies were notorious for using outdated systems that limited or wholeheartedly prevented access to vital information. It is risky to have the data in different systems when you begin bolting these systems together to pass required data between them. With a single system that houses data in one place instead of relying on bolt-ons, which cause silos, bio/pharmaceutical companies
**The Integrated Approach to Drug Development and Manufacturing**

An integrated program is a newer concept offered by CDMOs in which more of a project’s activities are placed with one supplier.

Efficiency, speed to market, and access to unique expertise are among the key benefits of partnering with a contract development and manufacturing organization (CDMO) that offers integrated, end-to-end services. Applying a fully integrated approach to drug discovery, development, manufacturing, packaging, and more—all with a single project manager as the primary point of contact and a single plan across multiple scientific disciplines—provides pharmaceutical and biotech innovators with tangible benefits. *Pharmaceutical Technology* recently spoke with Kevin Duffield, global head of project management at Piramal Pharma Solutions (PPS), about delivering successful product launches with the seamless transfer of technology, documentation, and materials across global sites.

**PHARMTECH:** How would you define an integrated services program?

**DUFFIELD:** Piramal has 14 manufacturing sites located around the world. Those sites typically specialize in one form of service to the pharma sector, like API manufacturing, solid oral dose or sterile fill/finish. For Piramal, an integrated program is a program where we use multiple sites to satisfy the needs of a single client program.

**PHARMTECH:** What are the advantages or benefits of an integrated services program to the sponsor?

**DUFFIELD:** One advantage for the sponsor is reduced business complexity. The sponsor has a single partner to help them work through the various program elements. It is possible to see timeline compression with an integrated project because you can sometimes take away complexities of shipments and movement of materials between sites. Another advantage is that you have a single project team covering the project, which allows for efficiencies in relationship and project management. A final advantage is, because you are now concentrating your business with your partner, there is a more strategic relationship between the parties that allows for more focus and attention by the provider to your needs.

**PHARMTECH:** Why is the ability to conduct an integrated services program important in today’s market?

**DUFFIELD:** It is kind of an old story, but speed to market is still a primary driver for new products being brought to market, and...
integration allows for the opportunity to overlap activities and increase speed. Another factor is that a lot of biotech firms make the decision to take their products directly to patients rather than selling off their assets once the concepts are proven. So, these companies are looking for partners that can provide broad technical, regulatory, and commercial capabilities to have one relationship take them to market in the shortest possible time. Another aspect is a surety of supply. As products become commercial, making sure that supply is never interrupted requires multiple manufacturing and redundant manufacturing sites. Large organizations with integrated programs can transfer those technologies internally and provide that surety of supply with backup manufacturing.

PHARMTECH: From a client’s perspective, what barriers do they need to overcome before committing to an integrated program?
DUFFIELD: In an integrated program, more of the project activities are placed with one supplier. So, the sponsor’s internal team needs to be aligned around the model. This is a newer concept in the history of CDMO businesses. It’s a strategic relationship rather than a tactical one, as common in the past.

PHARMTECH: What does PPS offer in integrated programs that makes its offering especially valuable to the customer?
DUFFIELD: Piramal has a system in which each of our sites has a project management team that facilitates the execution and client communications for that particular site’s activities. We add a layer of senior program managers who ensure our site business is aligned in a single plan and provide an escalation point for the client, should interconnections need to be improved. In addition, we have periodic business review meetings with the client that involve a Piramal senior manager. We view these as strategic relationships and treat them as such in terms of management, time, and oversight relating to our client’s expectations and our delivery performance. In some cases, these integrated programs offer access to unique technologies that Piramal has—particularly in the space of antibody drug conjugation, fill/finish, and most recently in the peptide synthesis area—where we can put together programs across technologies to make drug substances and bring them to dosage form at another site.

PHARMTECH: What does the future look like for integrated services programs?
DUFFIELD: Going back to 2005, there were integrated offerings that were early into the market. But those early providers fell on deaf ears. The market wasn’t ready for that kind of model. By 2015, most major CDMOs had some sort of integrated offering as the market came to the realization that they could save time and money with this model. I think by 2025, we will continue to see growth and companies, such as Piramal, add new technical capabilities or sites that allow us to provide more integrated programs. We will also see the emergence of true integrated practices where we don’t just have an integrated project plan but see how our sites can work together to remove time and redundant work as projects move from one stage to the next.

Piramal Pharma Solutions (PPS) is a CDMO offering end-to-end development and manufacturing solutions across the drug life cycle. We serve our customers through a globally integrated network of facilities in North America, Europe, and Asia. This enables us to offer a comprehensive range of services including drug discovery solutions, process & pharmaceutical development services, clinical trial supplies, commercial supply of APIs, and finished dosage forms. We also offer specialized services such as the development and manufacture of highly potent APIs, antibody-drug conjugations, sterile fill/finish, peptide products & services, and potent solid oral drug product. Our track record as a trusted service provider with experience across varied technologies makes us a partner of choice for innovator and generic companies worldwide.

For more information please visit: www.piramalpharmasolutions.com | Twitter | LinkedIn
A robust cleaning validation program is a crucial component in a good manufacturing practice (GMP)-compliant manufacturing facility. The quality systems supporting a GMP manufacturing facility are mutually dependent, and any component of the facility cannot be fully compliant if other components of the quality system are not equally compliant. As one component of an overall quality system, cleaning validation is just as important as every other quality function. Before cleaning validation can be executed, however, the following prerequisites need to be in place:

- The facility buildings need to be designed and have sufficient space for GMP activities.
- Building utilities, including air and water, that impact GMP operations need to be qualified.
- The quality assurance (QA) department must be an independent organization capable of detecting items that are not GMP compliant and be prepared to deal with any deficiencies.
- Document control must ensure that standard operating procedures (SOPs), protocols, and reports follow good document practices (GDPs) and are executed using controlled documents.
- Personnel must be trained and often qualified to perform the tasks they execute during the validation exercise.
- Equipment must undergo installation qualification (IQ), operation qualification (OQ), and performance qualification (PQ) before it is used for GMP functions.
- Test methods to support cleaning validation must be validated.
- Change control must be compliant so that all changes that impact GMP activities, including cleaning validation, are reviewed and approved before implementation.
- Manufacturing processes must be validated and shown to be in a state of control. In some instances, process validation and cleaning validation could be conducted using the same batches.
- A cleaning assessment should assess the status of the current equipment cleaning efforts and the extent of cleaning validation that is needed.

Cleaning validation requires a significant effort to design a strategic and effective program that is defendable with regulatory agencies. Of primary concern is what to validate. A robust selection of which product(s) and equipment to validate for cleaning is the cornerstone of a successful cleaning validation program. A strategy for selection of products and equipment for cleaning validation is presented.
• Cleaning development should result in a rugged, robust cleaning process that will clean all products from all equipment surfaces.

• Finally, cleaning procedures for each piece of equipment with sufficient detail to ensure consistent execution must be documented and preferably approved before cleaning validation begins.

Cleaning validation must be conducted for every cleaning process. A cleaning process is the activity of cleaning that is used to remove materials introduced into equipment as part of the manufacturing process stream (e.g., rinse, wash with detergent, rinse, purified water rinse, alcohol wipe). In contrast, a cleaning procedure is the step-by-step instruction with sufficient detail to ensure a consistent level of cleaning for a piece of equipment. Therefore, having a common cleaning process for all equipment is essential.

In parallel with the other cleaning validation prerequisites, before validation can commence, it must be decided what products to validate and what equipment will be used for the validation. If the validation execution is going to cover multiple products and equipment, it must be clearly stated, and a rationale must be documented that justifies the choices made for validation and the scope of products and equipment to be included.

Grouping products and equipment for cleaning validation is probably the most important strategic decision affecting the overall success of a program that can be validated and maintained over time using continued process verification (CPV). For every additional cleaning process, the hard-to-clean assessment, equipment grouping, product/equipment matrixing, and selection for validation must be repeated. The cleaning validation and cleaning maintenance efforts increase greatly, and the risk of non-compliance because of using the wrong cleaning process significantly increases.

Product grouping
Product grouping for cleaning validation can be implemented several ways. The easiest to define from a strategy standpoint but the hardest to implement and maintain is to validate every product in the facility portfolio. While feasible for a small facility (e.g., two to four products), validation of every product quickly becomes unmanageable and unsustainable as the size of the product portfolio grows.

Grouping by therapeutic or product family might somewhat limit the validation effort, but still will most likely result in too many cleaning validation candidates. Grouping by dosage form (e.g., tablets, liquids, hard and soft gel capsules) seems reasonable and sometimes necessary based on different equipment and cleaning process conditions (e.g., 60 °C water for soft-gel cleaning), but grouping different dosage forms (e.g., tablets and hard gel capsules) might be justifiable in a given facility.

The most efficient way to group products is using a worst-case approach to determine the product that presents the greatest challenge for cleaning validation.

Worst-case product
Hardest-to-clean product. A worst-case product approach has been accepted by regulatory agencies (1, 2). The European Commission (EC) Annex 15 (1) states, “Where a worst-case product approach is used as a cleaning validation model, a scientific rationale should be provided for the selection of the worst-case product.” It does not prescribe how to arrive at this rationale, and there are different ways to get there. The simplest rationale, which is often used, is to rely on the water solubility of the API in the formulation. This rationale is that the less soluble the API, the harder it is to clean that product. The primary problem with this rationale is that the API is not the majority component in most formulations. Additionally, excipients are often harder to clean than the APIs. Therefore, relying solely on the water solubility of the API is not a strong rationale for worst-case product, and there is a high risk of choosing the incorrect hardest-to-clean product.

A more thorough approach to a worst-case product for cleaning is to consider the API and excipient chemistry as well as physical characteristics of the formulation. Initially, assess all formulations for cleanability based on the physical properties of the formulation components using a semi-quantitative approach (3, 4). Physical properties that affect cleanability include solubility in water and hydrophobicity. This is a paper-based exercise and can provide useful quantitative cleanability ranking data relatively quickly and cheaply.

A second cleanability assessment can be based on experience of the plant operators, who use and clean the equipment. Their knowledge of what products are hard to clean is often invaluable and aids in their ownership of any cleaning validation effort. A survey of operators can also provide quantitative cleanability data leading to a relative ranking of products for cleaning.

The two assessments can be used to choose a limited selection of products to submit for laboratory cleanability assessment. Cleanability testing using formulations spiked onto stainless-steel coupons can be used to develop rugged cleaning conditions and provide another source of quantitative cleanability data.

The three assessments: formulation properties, personnel experience, and laboratory cleanability can be used to arrive at the product that is hardest-to-clean and the leading candidate for cleaning validation.

If the two assessments and laboratory data indicate the same hardest-to-clean product, the product selection for cleaning validation is obvious. Often there will be several candidates that could be the hardest-to-clean product. The two assessments typically overlap, but the specific order of hard-to-clean products can differ. The laboratory data will often be variable even for the replicates of the same product. In that case, all three sets of data are considered. If one hard-to-clean candidate is manufactured more frequently, it might be the best choice for the hardest-to-clean product. If this rationale is used to choose the hardest-to-clean product, it is prudent to include the other hard-to-clean candidates.
Where: ADE (µg/day) Product A
Batch size (doses or g) Product B
Max. Daily Dose (doses/day or g/day) Product B
Swab area (cm²/swab)
SA = Surface Area (cm²) of the equipment being cleaned
RF = Recovery Factor (decimal)
The ARL should be calculated for every product, and the product with the lowest ARL should be the target of cleaning validation.
The hardest-to-clean product and the product with the lowest ARL should be considered for cleaning validation. If the same product fulfills both criteria, again the selection is obvious. However, if the two criteria point to two different products, there are two options. The first and recommended option is to validate the hardest-to-clean product with a target acceptance criteria of the lowest ARL. If you can validate cleaning of the hardest-to-clean product to levels below the lowest cleaning limit, all products are considered validated. The second option is to validate both products. However, the second option will lead to additional work because the hardest-to-clean product was validated to a higher ARL.

Equipment grouping
Equipment grouping has also been accepted by regulatory agencies (1, 2). EMA Annex 15 (1) states, “Where similar types of equipment are grouped together, a justification of the specific equipment selected for cleaning validation is expected.” Therefore, equipment grouping should follow justifiable criteria related to the ability to clean the equipment. The following criteria can be used as the basis for the grouping:
- Similar equipment function. Equipment that performs the same function (e.g., tablet press group, blender group).
- Different size equipment. Equipment from the same functional group but of different size can be grouped. They have the same cleaning process, and although the larger equipment takes longer to clean, the cleaning is essentially the same.
- Similar geometry. Different equipment with similar geometry for cleaning may be grouped (e.g., comil, Fitzmill).
- Degree of disassembly. Different equipment can be grouped if cleaning accessibility is comparable. Disassembly of equipment for cleaning will also be considered for accessibility. If two similar equipment with different sizes are disassembled so that the parts are cleaned the same way, the equipment may be grouped.
Equipment grouping needs to be done strategically in parallel with the product grouping. The objective should be that equipment grouping does not significantly add to the cleaning validation effort. For example, a large and a small piece of the same unit operation (e.g., V-blender) might be considered as sufficiently different for cleaning as to warrant separate validation. Or grouping could decide to bracket each group of equipment and validate the largest and smallest equipment in the group. Either strategy could be problematic. If the equipment chosen for cleaning validation does not process the worst-case product, then the effort to execute cleaning validation will increase significantly and serve to make a successful cleaning validation program unachievable.

Depending on the number of unit operations, it might be advisable to group more aggressively and combine seemingly different types of equipment (e.g., tablet presses and capsule fillers). This strategy could work if both types of equipment are disassembled for cleaning. In such a case, the equipment would be presented for cleaning as discrete parts with similar issues for cleaning.

Regardless of the strategy used for equipment grouping, documentation needs to describe the strategy employed, the groups of equipment, and every piece of equipment included in each group. Validate cleaning using one representative piece of equipment from a group, then all other equipment in the group are considered validated. Once cleaning validation is complete, include other equipment from the group in the CPV effort.

Once product grouping and equipment grouping are complete, the strategy for the first cleaning validation execution can be discussed. Cleaning validation execution needs to address the worst-case product(s) and all equipment groups.

Product/equipment matrix
Using the knowledge of the hard-to-clean products coupled with equipment grouping, review the equipment train for all the products in the facility. The equipment train used to manufacture the worst case is validated for cleaning against the lowest cleaning limit. If the worst-case product is manufactured using equipment covering all equipment groups, then a single cleaning validation study would cover all products and all equipment. If the worst-case product does not cover all equipment groups, a second validation using the hardest-to-clean product that is manufactured on the remaining equipment groups is needed.
Packaging

Cleaning validation for packaging equipment is conducted separately from the manufacturing equipment. This approach is preferable for several reasons. First, packaging operations are often physically separate from manufacturing operations. Second, scheduling of packaging equipment is not connected with manufacturing schedules, so coordination of a cleaning validation study between the two areas is difficult, while separate cleaning validation studies can be more easily controlled and executed.

Third, the hardest-to-clean product for manufacturing might not be the hardest-to-clean product for packaging, particularly if it is a film-coated tablet. Formulations that are not film coated tend to be dustier on a packaging line and leave higher levels of residue on the packaging equipment, which presents a greater challenge for cleaning.

Case study: hardest-to-clean product

Personnel experience. For a medium-size company with a portfolio of 10 products, the hardest-to-clean product was evaluated using two parallel processes. Operations personnel were polled per an approved protocol to identify the three hardest-to-clean products based on their experience. A greater weight was given to products that were ranked as more hard-to-clean as a way to differentiate the three chosen products. A response of first was given five points; a second response given three points, and a third response given one point. The questionnaire responses are tabulated in Table I. The hardest-to-clean product based on personnel feedback was Product A.

Formulation composition. In addition, the formulations of the products were assessed based on their physical and chemical properties. Each formulation component was given a cleanliness factor based on these properties and multiplied by the percentage of the formulation component. The formulation assessment for the products is shown in Table II. The same assessment was performed for the other products in the portfolio, and the results are shown in Table III.

Table I. Hard-to-clean product per personnel experience.

<table>
<thead>
<tr>
<th>Department: B (Blending)</th>
<th>C (Compressing)</th>
<th>P (Packaging)</th>
<th>C (Film coating)</th>
<th>Total Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product</td>
<td>1st (x5)</td>
<td>2nd (x3)</td>
<td>3rd (x1)</td>
<td></td>
</tr>
<tr>
<td>Product A</td>
<td>BBCCCCBBCCCCCP-PCBPPPPP</td>
<td>PPP</td>
<td>PPP</td>
<td>122</td>
</tr>
<tr>
<td>Product B</td>
<td>CBBCPBBBC</td>
<td>CCCCBBCCCCPPBCBPPPPP</td>
<td>PPCB</td>
<td>96</td>
</tr>
<tr>
<td>Product C</td>
<td>PP</td>
<td>BCBCPBBBBBP</td>
<td>BCP</td>
<td>40</td>
</tr>
<tr>
<td>Product D</td>
<td>BP</td>
<td>PPBP</td>
<td>CBBBPPPPPPBP</td>
<td>34</td>
</tr>
<tr>
<td>Product E</td>
<td>BBB</td>
<td>B</td>
<td>C</td>
<td>19</td>
</tr>
<tr>
<td>Product F</td>
<td>CCC</td>
<td>BBC</td>
<td>BCBB</td>
<td>13</td>
</tr>
<tr>
<td>Product G</td>
<td>PP</td>
<td>B</td>
<td>BBB</td>
<td>11</td>
</tr>
<tr>
<td>Product H</td>
<td>B</td>
<td>B</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Product I</td>
<td>B</td>
<td>B</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Product J</td>
<td>B</td>
<td>B</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Product K</td>
<td>C</td>
<td>C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table II. Formulation composition cleanability factors.

<table>
<thead>
<tr>
<th>Product A</th>
<th>Amount per unit (mg)</th>
<th>% Formulation</th>
<th>Cleanability Factor</th>
<th>Cleanability Component</th>
<th>Product B</th>
<th>Amount per unit (mg)</th>
<th>% Formulation</th>
<th>Cleanability Factor</th>
<th>Cleanability Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>6.0</td>
<td>4.3</td>
<td>1</td>
<td>4</td>
<td>API</td>
<td>8.0</td>
<td>4.0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Lactose</td>
<td>25.0</td>
<td>17.9</td>
<td>1</td>
<td>18</td>
<td>Microcrystalline Cellulose</td>
<td>170.0</td>
<td>85.0</td>
<td>3</td>
<td>255</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>25.0</td>
<td>17.9</td>
<td>3</td>
<td>54</td>
<td>Corn Starch</td>
<td>10.0</td>
<td>5.0</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose</td>
<td>60.0</td>
<td>42.9</td>
<td>4</td>
<td>171</td>
<td>Sugar Spheres</td>
<td>6.0</td>
<td>3.0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Silicon Dioxide</td>
<td>0.5</td>
<td>0.4</td>
<td>2</td>
<td>1</td>
<td>Stearic Acid</td>
<td>5.0</td>
<td>2.5</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Talc</td>
<td>5.7</td>
<td>4.0</td>
<td>3</td>
<td>12</td>
<td>Magnesium Stearate</td>
<td>1.0</td>
<td>0.5</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>1.5</td>
<td>1.1</td>
<td>4</td>
<td>4</td>
<td>200.0</td>
<td>100.0%</td>
<td>Total</td>
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<tr>
<td>Eudragit</td>
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<td>4</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triethyl Citrate</td>
<td>1.485</td>
<td>1.1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>140.0</td>
<td>100.0%</td>
<td></td>
<td>Total 310</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The hardest-to-clean product from a formulation composition standpoint was Product C.

**Laboratory cleanability.** From the personnel experience assessment, the hardest-to-clean products, in order, were Products A, B, C, and D. From the formulation composition assessment, Products C, E, A, and D are the hardest-to-clean products. To be conservative, Products A, B, C, D, and E were submitted for laboratory coupon cleanability studies. Coupons were spiked with slurry samples of formulation, dried, and then subjected to four cleaning actions using alkaline detergent: agitated immersion, spray impingement, cascade, and scrubbing. Time and water temperature were

### Table II. Formulation composition cleanability factors (Continued).

<table>
<thead>
<tr>
<th>Product</th>
<th>Amount per unit (mg)</th>
<th>% Formulation</th>
<th>Cleanability Factor</th>
<th>Cleanability Component</th>
<th>Product</th>
<th>Amount per unit (mg)</th>
<th>% Formulation</th>
<th>Cleanability Factor</th>
<th>Cleanability Component</th>
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<tbody>
<tr>
<td>API</td>
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<td>4</td>
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<td>API</td>
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<td>3.0</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Corn Starch</td>
<td>60.56</td>
<td>16.4</td>
<td>2</td>
<td>33</td>
<td>Microcrystalline Cellulose</td>
<td>314.70</td>
<td>95.4</td>
<td>3</td>
<td>286</td>
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</tr>
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<td>Magnesium Stearate</td>
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<td><strong>370.0</strong></td>
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<td>FD&amp;C Red</td>
<td>0.40</td>
<td>0.1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<table>
<thead>
<tr>
<th>Product</th>
<th>Amount per unit (mg)</th>
<th>% Formulation</th>
<th>Cleanability Factor</th>
<th>Cleanability Component</th>
<th>Product</th>
<th>Amount per unit (mg)</th>
<th>% Formulation</th>
<th>Cleanability Factor</th>
<th>Cleanability Component</th>
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<td>8</td>
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<tr>
<td>Microcrystalline Cellulose</td>
<td>78.20</td>
<td>52.1</td>
<td>3</td>
<td>156</td>
<td>Lactose</td>
<td>60.0</td>
<td>50.8</td>
<td>1</td>
<td>51</td>
</tr>
<tr>
<td>Hydroxypropyl Methylcellulose</td>
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</tr>
<tr>
<td>Talc</td>
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<td>1.0</td>
<td>3</td>
<td>3</td>
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<td>16.9</td>
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<td>34</td>
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<tr>
<td>Hydroxypropyl Methylcellulose</td>
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<td>0.2</td>
<td>4</td>
<td>1</td>
<td>Sodium Starch Glycolate</td>
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<td>3.0</td>
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<td>6</td>
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<td><strong>150.00</strong></td>
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<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Opadry White</td>
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<table>
<thead>
<tr>
<th>Product</th>
<th>Amount per unit (mg)</th>
<th>% Formulation</th>
<th>Cleanability Factor</th>
<th>Cleanability Component</th>
<th>Product</th>
<th>Amount per unit (mg)</th>
<th>% Formulation</th>
<th>Cleanability Factor</th>
<th>Cleanability Component</th>
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<tr>
<td>API</td>
<td>5.000</td>
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<td>154</td>
<td>API</td>
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<td>60.6</td>
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<td>2</td>
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<td>185.82</td>
<td>33.8</td>
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<tr>
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<td>2</td>
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<td>3.0</td>
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<tr>
<td>Stearic Acid</td>
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<td>4</td>
<td>4</td>
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</table>

<table>
<thead>
<tr>
<th>Product</th>
<th>Amount per unit (mg)</th>
<th>% Formulation</th>
<th>Cleanability Factor</th>
<th>Cleanability Component</th>
<th>Product</th>
<th>Amount per unit (mg)</th>
<th>% Formulation</th>
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<td>154</td>
<td>API</td>
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<td>2</td>
<td>2</td>
<td>Silicon Dioxide</td>
<td>2.35</td>
<td>0.6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>84.939</td>
<td>18.1</td>
<td>3</td>
<td>54</td>
<td>Microcrystalline Cellulose</td>
<td>82.44</td>
<td>17.5</td>
<td>3</td>
<td>53</td>
</tr>
<tr>
<td>Croscarmellose Sodium</td>
<td>9.40</td>
<td>2.0</td>
<td>2</td>
<td>4</td>
<td>Croscarmellose Sodium</td>
<td>9.40</td>
<td>2.0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>4.70</td>
<td>1.0</td>
<td>4</td>
<td>4</td>
<td>Stearic Acid</td>
<td>4.70</td>
<td>1.0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>470.0</strong></td>
<td>100.0%</td>
<td><strong>Total</strong></td>
<td>218</td>
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<td></td>
<td><strong>470.0</strong></td>
<td>100.0%</td>
<td><strong>Total</strong></td>
<td>217</td>
</tr>
</tbody>
</table>
monitored with visual cleanliness as the endpoint. The results for the laboratory coupon cleanability study are shown in Table IV. For each cleaning action, all residues were cleaned using a common detergent concentration and temperature. The longest time required to clean residues were for Products C and E as three of the cleanability tests, although Product A took longer for manual scrubbing.

**Hardest-to-clean product selection.** The data generated for the hardest-to-clean product were not completely definitive. One could argue a convincing case to use Product A or Product C as the hardest-to-clean product with a less compelling case for Product E as shown in Table V. However, before a worst-case product decision was made, the cleaning limits were calculated and combined with the hard-to-clean data.

**Lowest cleaning limit product.** The ARL was calculated using Equation 1 for each of the 10 products against the other nine products manufactured in the facility. The parameters that make up the ARL calculation are shown in Table VI. The calculated ARL results for all product combinations are shown in Table VII. The minimum ARL was determined for each product as a target for cleaning validation activities.

The overall lowest cleaning limit of 140 µg/swab was for Product I. Product I is not a candidate for the hardest-to-clean product. However, the product that is chosen for cleaning validation should have a validation acceptance criterion of 140 µg/swab to validate all products.

Based on the ARL calculations, all cleaning limits are likely higher than the visible residue limit (VRL) for the product (6–9). For this case study, it is value added to establish the VRLs for each product as an additional layer of process control data. Evaluate the margin between the VRL and the ARL. This result is an easily discerned margin of safety and indicative of the risk of having a piece of equipment fail cleaning the ARL from the patient safety perspective. Because every piece of equipment is visually inspected after cleaning, an ongoing, quantitative dataset for CPV can be established.

**Worst-case product for cleaning validation.** At this point, a worst-case product for cleaning validation could be chosen from the available product cleanability and ARL data. However, the remaining factors affecting the worst-case product selection include manufacturing equipment grouping, product/equipment matrix, and the manufacturing schedule.

**Equipment grouping.** In parallel with the worst-case product determination, equipment grouping was determined for all product contact manufacturing equipment. Although it could be argued that all equipment that is disassembled and manually cleaned could be in one group, it is easier to defend and simpler to group most equipment by their unit operation. Equipment can be assigned to the following groups: sieve, mill, blender, granulator, tablet press/encapsulator, metal detector, deduster, film coater, and tank groups. Equipment grouping strategy can be challenged; therefore, a detailed justification is necessary for any questions that arise.

**Grouping issues: granulators.** If the hardest-to-clean product(s) uses both high-shear and fluid bed granulators, having them in separate groups is straight-forward. If the hardest-to-clean product(s) only use one of the granulators,

### Table III. Hard-to-clean product per formulation composition.

<table>
<thead>
<tr>
<th>Product</th>
<th>Total Cleanability Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product C</td>
<td>364</td>
</tr>
<tr>
<td>Product E</td>
<td>327</td>
</tr>
<tr>
<td>Product A</td>
<td>310</td>
</tr>
<tr>
<td>Product D</td>
<td>295</td>
</tr>
<tr>
<td>Product B</td>
<td>284</td>
</tr>
<tr>
<td>Product H</td>
<td>238</td>
</tr>
<tr>
<td>Product G</td>
<td>220</td>
</tr>
<tr>
<td>Product I</td>
<td>218</td>
</tr>
<tr>
<td>Product J</td>
<td>217</td>
</tr>
<tr>
<td>Product F</td>
<td>165</td>
</tr>
</tbody>
</table>

### Table IV. Hard-to-clean product per laboratory coupon cleanability results.

<table>
<thead>
<tr>
<th>Cleaning Action</th>
<th>Agitated Immersion</th>
<th>Spray Wash (impingement)</th>
<th>Cascade Scrubbing</th>
<th>Scrubbing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detergent</td>
<td>Alkaline</td>
<td>Alkaline</td>
<td>Alkaline</td>
<td>Alkaline</td>
</tr>
<tr>
<td>Concentration</td>
<td>1% v/v</td>
<td>1% v/v</td>
<td>1% v/v</td>
<td>3% v/v</td>
</tr>
<tr>
<td>Product A</td>
<td>30 min/45 °C</td>
<td>15 min/60 °C</td>
<td>15 min/60 °C</td>
<td>60 sec/45 °C</td>
</tr>
<tr>
<td>Product B</td>
<td>30 min/45 °C</td>
<td>15 min/60 °C</td>
<td>15 min/60 °C</td>
<td>15 sec/45 °C</td>
</tr>
<tr>
<td>Product C</td>
<td>30 min/45 °C</td>
<td>30 min/60 °C</td>
<td>30 min/60 °C</td>
<td>45 sec/45 °C</td>
</tr>
<tr>
<td>Product D</td>
<td>30 min/45 °C</td>
<td>15 min/60 °C</td>
<td>15 min/60 °C</td>
<td>45 sec/45 °C</td>
</tr>
<tr>
<td>Product E</td>
<td>30 min/45 °C</td>
<td>30 min/60 °C</td>
<td>30 min/60 °C</td>
<td>45 sec/45 °C</td>
</tr>
</tbody>
</table>

### Table V. Hard-to-clean products.

<table>
<thead>
<tr>
<th>Personnel experience</th>
<th>Formulation composition</th>
<th>Coupon cleanliness</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>B</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td>C</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>B</td>
</tr>
</tbody>
</table>
then a single granulator group might be more practical. With a single equipment group, there could be some disagreement in assigning a high-shear granulator with a Glatt fluid air granulator. Both are granulators, but their modes of granulating are significantly different, and it could be argued that they present different cleaning challenges. But, if both types of equipment are disassembled for cleaning, the differences in cleaning become less apparent and grouping becomes more defendable.

The immediate question is “why try to group them if there will be push-back?” If the granulator group is split into two groups, and the worst-case product is processed on the high-shear granulator, then the fluid air granulator would need to be validated for cleaning under a separate study of at least three consecutive batches. If all other equipment groups are already covered for cleaning validation, then running validation for one piece or group of equipment does not seem value added.

**Grouping issues:** Encapsulator. An encapsulator provides an example of a potential outlier for equipment grouping. An encapsulator is a separate unit operation with a particular set of cleaning challenges, but hard-gel capsule products are generally not as common as tablet formulations, and a capsule blend is not hard to clean compared to tablets with binders and film coating.

To avoid a separate cleaning validation for a piece of equipment processing relatively easy-to-clean products, it would need to be grouped with other equipment with the same or similar cleaning challenges. An encapsulator could be grouped with tablet presses because both types of equipment are disassembled for manual cleaning. If grouping is attempted, it would be prudent to add detail to the encapsulator cleaning procedure targeting any capsule cavities that are present in the equipment or any other details particular to the encapsulator.

**Product/equipment matrix.** Once equipment grouping was complete, the product/equipment matrix was constructed as shown in Table VIII. The most straightforward approach would be if the hardest-to-clean product were manufactured using all equipment groups. However, because no product covers all equipment groups in Table VIII, the hardest-to-clean product as determined previously was used. Product C uses sieves, both high-shear and fluid-air granulators, blenders, tablet presses, metal detectors, and dedusters but does not use mills or film coaters. Therefore, a second cleaning validation was necessary to cover the other equipment groups.

<table>
<thead>
<tr>
<th>Product</th>
<th>ADE (µg/day)</th>
<th>Maximum Daily Dose (doses/day)</th>
<th>Batch Size (doses)</th>
<th>Surface Area (cm²)</th>
<th>Swab Area (cm²/swab)</th>
<th>Recovery Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>100</td>
<td>2</td>
<td>800,000</td>
<td>60783</td>
<td>25</td>
<td>0.95</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>2</td>
<td>400,000</td>
<td>60783</td>
<td>25</td>
<td>0.92</td>
</tr>
<tr>
<td>C</td>
<td>30</td>
<td>6</td>
<td>2,000,000</td>
<td>178274</td>
<td>25</td>
<td>0.89</td>
</tr>
<tr>
<td>D</td>
<td>400</td>
<td>2</td>
<td>3,000,000</td>
<td>250466</td>
<td>25</td>
<td>0.85</td>
</tr>
<tr>
<td>E</td>
<td>80</td>
<td>2</td>
<td>7,000,000</td>
<td>229138</td>
<td>25</td>
<td>0.93</td>
</tr>
<tr>
<td>F</td>
<td>90</td>
<td>3</td>
<td>7,000,000</td>
<td>229138</td>
<td>25</td>
<td>0.93</td>
</tr>
<tr>
<td>G</td>
<td>25</td>
<td>6</td>
<td>1,100,000</td>
<td>115868</td>
<td>25</td>
<td>0.90</td>
</tr>
<tr>
<td>H</td>
<td>50</td>
<td>6</td>
<td>1,100,000</td>
<td>115868</td>
<td>25</td>
<td>0.84</td>
</tr>
<tr>
<td>I</td>
<td>70</td>
<td>2</td>
<td>700,000</td>
<td>81493</td>
<td>25</td>
<td>0.88</td>
</tr>
<tr>
<td>J</td>
<td>300</td>
<td>2</td>
<td>1,400,000</td>
<td>104719</td>
<td>25</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*Total equipment product contact surface area

<table>
<thead>
<tr>
<th>Product</th>
<th>Min. ARL</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>200</td>
<td>NA</td>
<td>200</td>
<td>13024</td>
<td>58610</td>
<td>136757</td>
<td>91171</td>
<td>7163</td>
<td>7163</td>
<td>13676</td>
<td>27351</td>
</tr>
<tr>
<td>B</td>
<td>6937</td>
<td>15136</td>
<td>NA</td>
<td>12613</td>
<td>56759</td>
<td>132438</td>
<td>88292</td>
<td>6937</td>
<td>6937</td>
<td>13244</td>
<td>26488</td>
</tr>
<tr>
<td>C</td>
<td>180</td>
<td>1498</td>
<td>180</td>
<td>NA</td>
<td>5616</td>
<td>13105</td>
<td>8737</td>
<td>686</td>
<td>686</td>
<td>1310</td>
<td>2621</td>
</tr>
<tr>
<td>D</td>
<td>800</td>
<td>13575</td>
<td>800</td>
<td>11312</td>
<td>NA</td>
<td>118779</td>
<td>79186</td>
<td>6222</td>
<td>6222</td>
<td>11878</td>
<td>23756</td>
</tr>
<tr>
<td>E</td>
<td>160</td>
<td>3247</td>
<td>160</td>
<td>2706</td>
<td>12176</td>
<td>NA</td>
<td>18941</td>
<td>1488</td>
<td>1488</td>
<td>2841</td>
<td>5682</td>
</tr>
<tr>
<td>F</td>
<td>270</td>
<td>3653</td>
<td>270</td>
<td>3044</td>
<td>13698</td>
<td>31962</td>
<td>NA</td>
<td>1674</td>
<td>1674</td>
<td>3196</td>
<td>6392</td>
</tr>
<tr>
<td>G</td>
<td>150</td>
<td>1942</td>
<td>150</td>
<td>1618</td>
<td>7282</td>
<td>16991</td>
<td>11328</td>
<td>NA</td>
<td>890</td>
<td>1699</td>
<td>3398</td>
</tr>
<tr>
<td>H</td>
<td>300</td>
<td>3625</td>
<td>300</td>
<td>3021</td>
<td>13593</td>
<td>31717</td>
<td>21145</td>
<td>1661</td>
<td>NA</td>
<td>3172</td>
<td>6343</td>
</tr>
<tr>
<td>I</td>
<td>140</td>
<td>7559</td>
<td>140</td>
<td>6299</td>
<td>28346</td>
<td>66141</td>
<td>44094</td>
<td>3465</td>
<td>3465</td>
<td>NA</td>
<td>13228</td>
</tr>
<tr>
<td>J</td>
<td>600</td>
<td>27216</td>
<td>600</td>
<td>22680</td>
<td>102059</td>
<td>238137</td>
<td>158758</td>
<td>12474</td>
<td>12474</td>
<td>23814</td>
<td>NA</td>
</tr>
</tbody>
</table>
Product A uses sieves, mills, blenders, tablet presses, metal detectors, dusters, and film coaters. Using two of the designated hard-to-clean products, C and A, all equipment groups were covered.

**Manufacturing schedule.** The manufacturing schedule was reviewed to ascertain the frequency of manufacturing for the worst-case product candidates. The more frequent a product is manufactured, the more opportunities there are for execution of cleaning validation. The upcoming manufacturing schedule is shown in Table IX, with the number of batches of each manufactured product indicated. For example, two batches of Product A will be manufactured during week one of the first month.

**Cleaning validation schedule.** Based on the selection of the hard-to-clean products (Products A and C), the target cleaning limit (140 μg/swab), and the upcoming manufacturing schedule, Product C will be scheduled for cleaning validation because it is to be manufactured less frequently but on an ongoing basis. Ideally, validation will be scheduled after each four-batch campaign with the completion of cleaning validation targeted by the end of month two.

Once the schedule for Product C is firm, Product A will be scheduled. In the best case, if sufficient resources are available, including sampling and laboratory testing, then cleaning validation of Product A will be initiated immediately. In the worst-case, cleaning validation for Product A will not commence until after Product C is completed.

Cleaning validation of Products A and C overlap for the sieve, blender, tablet press, duster, and metal detector equipment groups. Based on the cleaning validation rationale presented, these groups will only need to be tested for one product. If everything passes, they would be validated for all products. However, if cleaning, sampling, and testing can be executed and reported expeditiously, it would be advantageous to test all equipment groups for both products. This approach provides a greater number of cleaning data points to demonstrate the ruggedness of the cleaning process more clearly.

If cleaning, sampling, or testing is routinely delayed after manufacturing is complete, the value of the extra data might be offset by the time and coordination challenges for the extended timetable.

**Packaging.** Cleaning validation for packaging equipment was executed as a separate study from the manufacturing equipment. Coordination between the two areas is often offset, in that packaging can occur weeks after manufacturing, and closing out a coordinated study covering both areas is problematic. Additionally, the hardest-to-clean product for packaging is most likely to be an uncoated tablet, because coated tablets and capsules leave less dust than an uncoated tablet. If both products A and C are coated, then the hardest to clean uncoated product is chosen for cleaning validation.

**Conclusion**

Grouping products and equipment are crucial prerequisites for cleaning validation and are probably the most important strategic decision affecting the overall success of a program that can be validated and maintained over time. The factors that go into the grouping (i.e., hard-to-clean products, cleaning limits, equipment grouping, product/equipment matrix, and manufacturing schedule) are interrelated and need to be balanced to arrive at the best fit for any given facility.

### References

5. ISPE. *Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP),* Section 16.2., 2015.

Richard Forsyth is a Principal Consultant with Forsyth Pharmaceutical Consulting.
Outsourcing

Developing the Best Formulation Partnership

Felicity Thomas

Collaborative partnerships can foster success in formulation development projects.

The formulation development outsourcing market is expected to grow at a compound annual rate of 7.2% between 2021 and 2026 (1). Major factors driving growth in this sector are expected to be increasing innovation of novel drugs due to patent expirations, a focus on developing poorly water-soluble compounds that require bioavailability enhancement, and overcoming the risks associated with development (1).

To learn more about the industry trends, common requests, biggest challenges, and benefits of outsourced formulation services, Pharmaceutical Technology spoke with a panel of experts. The panel includes Sabine Hauck, senior vice-president of Corporate Development, Leukocare; Alexander Faude, director Process Science, Downstream Processing, and Marvin Kadressch, director Process Science, Upstream Processing, both at Rentschler Biopharma; and Stefan Heindl, business development manager, Coriolis Pharma.

Industry trends
PharmTech: Could you provide some insight into industry trends that have been impacting the formulation development outsourcing market in recent years?

Hauck (Leukocare): Formulation development has gained momentum in recent years. Beyond the stabilization of the drug substance by molecular design, formulation development is a key opportunity in the process of drug product development that offers potential to generate further commercial value. To accommodate this trend, continuous expansion of formulation expertise is recommended so that client requirements for viral vector stabilization, vaccines and advanced therapy medicinal products (ATMPs), higher drug substance concentration, longer storage time at higher temperature, or creation of new intellectual property can be met. For example, Leukocare has successfully managed the development of targeted formulations by applying its database and algorithm-based formulation development approach.

Faude (Rentschler Biopharma): The value and benefits of early formulation development have increasingly gained recognition and acceptance across the industry. Hence, companies are looking closely at all aspects of biopharmaceutical production, from start to finish, to identify opportunities for timeline optimization. As a result, it has been the experience of Rentschler Biopharma that the trend of collaborating with external experts in formulation development is picking up.

Heindl (Coriolis Pharma): Coriolis began specializing in formulation development in 2008 when formulation was often not the highest priority during drug product development. This has changed and the formulation development outsourcing market has been in a sustainable growth phase for several years now. Daily work at Coriolis has demonstrated a clear trend towards more complex products, for example, highly concentrated liquid formulations (HCLFs) with protein concentrations of up to 300 mg/mL or higher, or novel protein formats that require dedicated scientifically driven formulation strategies, rather than standard platform approaches. Also, requests regarding vaccine development, particularly in the context of the ongoing coronavirus pandemic have increased in the past two years; nucleic acid-based therapeutics gain more and more importance. However, the most important trend in my view is the increase in ATMPs, such as viral-vectors, oncolytic viruses, and other genetically modified organisms, that are entering the scene. Many of these products require new and innovative formulation approaches, analytical strategies, as well as special facilities.
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Service requests
PharmTech: What type of formulation work is more commonly outsourced and has the type of project changed over the years?

Heindl (Coriolis Pharma): Formulation development services are requested across all stages of development, from early-stage pre-formulation work to late-stage reformulation projects, in-use studies, or trouble-shooting activities. Two different trends have been seen at Coriolis. One trend is an increasing demand for the outsourcing of complete packages, including pre-clinical tox manufacturing and good manufacturing practice (GMP) manufacturing (e.g., for first clinical phases of the developed formulation). To meet this demand, it is important to expand the service portfolio, for example, by expanding tox-batch manufacturing capabilities for liquid and lyophilized formulations. Moreover, it is necessary to seek out and maintain partnerships with other established players in the field to cover GMP manufacturing. These close partnership networks allow for comprehensive outsourcing packages to be offered while keeping the number of interfaces for the client low. The second one is outsourcing of highly challenging and individual formulation tasks that require a scientific background and a very specialized formulation approach. For this trend, it is important that the service provider has the required track record, experience, and scientific background for the task.

Hauck (Leukocare): All kinds of formulation development are outsourced, depending on the needs of the sponsors. Early pre-formulation development supports stability already in tox studies and allows de-risking success of a clinical candidate due to stability issues. Fully fledged formulation development is outsourced in all stages of clinical development, depending on the clinical development strategy. Even if the asset is planned for out-licensing after clinical stage, a well-designed formulation will increase the value of the drug product package. In general, time has become more critical over the years, while quality requirements are still increasing. That’s why it is key to outsource formulation development to an expert contract development and manufacturing organization (CDMO) developing high-quality formulations in an accelerated period.

Biggest challenges
PharmTech: What are the biggest challenges for outsourcing partners when approaching/working on a formulation project with a sponsor company?

Faude (Rentschler Biopharma): When collaborating with a sponsor company, the success of early formulation development depends heavily on material that has been generated via ‘preliminary’ processes. These processes are themselves undergoing development and optimization. Hence, they are bound to change right until first current GMP production for clinical development. Moreover, the process may undergo further improvement or adaptations for market approval. Therein lies a challenge for the outsourcing partner but also great benefit for the sponsor company’s product. This is because these adaptations can be sequentially incorporated into formulation development to further maximize product potential.

Kadisch (Rentschler Biopharma): The role of the outsourcing partner as an expert consultant for the sponsor company is also very crucial. It is essential that the outsourcing partner sees the project as an extension of their own operations and advises the client from this point of view. Aspects such as which formulation best suits the molecule in question, subsequent implementation and regular project status updates are central to a successful collaboration.

Heindl (Coriolis Pharma): Well, every client is different, and each molecule of interest and target product profile require a dedicated strategy. A common aspect is that the timeline is always key. While in early stages, drug substance availability is often a challenge, though mostly manageable, real challenges arise when formulation development is squeezed in between other development activities such as drug substance development and drug product manufacturing. Depending on the drug substance and client, knowledge about the stability profile of the API can be very scarce. Due to all these reasons, an understanding of the specific requirements of each client, a smart, scientifically-sound design with built-in flexibility and a clear expectation management is important.

Hauck (Leukocare): Formulation development is always linked to other aspects of product development, such as process development for upstream processing and downstream processing, pharmaceutical development or fill/finish, logistics, and product administration. It is important to consider interactions and interdependencies.

Overcoming challenges
PharmTech: How do outsourcing partners overcome these challenges?

Heindl (Coriolis Pharma): At Coriolis, for example, a lot of investment is made into the upfront discussions with the client to understand the particular needs for the project. In combination with our experience as a formulation specialist, these discussions provide the basis for a tailored and scientifically-sound proposal considering all specific requirements of the client. During an ongoing project, open and transparent discussions on a regular basis (e.g., in weekly or biweekly meetings) help to align development efforts and allow for quick reactions to scope changes or unforeseen issues. Especially during early-stage projects, a high degree of flexibility is often needed, requiring a specific skill set of the team working on the projects to quickly provide a stable formulation backed-up by a suitable analytical toolbox and stability data.

Kadisch (Rentschler Biopharma): A very helpful solution to tackle these challenges access to a large database, as well as experience with different classes of molecules. This includes tools like in-silico modeling and more targeted wet-lab trials. This can significantly accelerate the development of suitable formulations for the sponsor company’s product.

Hauck (Leukocare): Requests for faster formulation development should be met with innovative strategies; extending the analytical toolbox can help to save time and material. Moreover,
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tomation in formulation and analytical technology supports parallelization and thus supports higher turn-over. Making use of bioinformatic expertise leads to timesaving as well as quality improvement for projects.

Faude (Rentschler Biopharma): To overcome these challenges a review of the ‘fit of the formulation to the product’ can be continuously addressed during preclinical and clinical product development. This allows one to quickly identify ‘constellations of fitness’ that can then be focused on to further optimize both formulation and the end product.

Key benefits
PharmTech: What are the key benefits for outsourcing formulation development?
Kadisch (Rentschler Biopharma): Based on the experiences of projects undertaken by Rentschler Biopharma, it is believed that the seamless integration of formulation development into the entire product life cycle and timelines harbors two key benefits: it allows for exceptionally efficient product optimization and ensures that project delays are avoided. Furthermore, the consultation provided by the outsourcing partner is key in defining the best-fit for both client and product.

Faude (Rentschler Biopharma): Outsourcing partners, such as Rentschler Biopharma, have holistic offerings where the entire process and formulation development is offered in an optimally integrated form. In this manner, clients can greatly benefit from the experience and expertise of the outsourcing partner for an ‘improved’ product within optimal timeframes.

Hauck (Leukocare): Essentially, it enables companies to gain access to best-in-class formulation development. For smaller companies with few products, an external formulation development team can be used just for the short period of time needed and avoids the efforts required of recruitment and training. Typically, it is much easier for an outsourcing partner to answer short notice demand on higher required effort. Formulation development can be performed whenever it suits best.

Haundl (Coriolis Pharma): In the context of the increasing complexity mentioned before, the outsourcing of such projects allows for both client and product.

Manufacturing — Contin. from page 41

can avoid one of the key pitfalls of the past. By streamlining serialization data, drug-makers can also better keep track of expiration dates, which is especially important for medications that have a short shelf life.

Business benefits beyond compliance
Bio/pharmaceutical supply chains are fast and have come a long way since the first prescription drugs were invented, but they could be faster. Thus, drug-makers need to optimize sales through tighter process control and adherence to set standards. The same processes used for compliance with serialization and traceability regulations can enable collaboration, creating more transparency for stakeholders, and improving the ecosystem of the supply chain.

Traceability, security, and regulatory compliance can be taken to a higher level when serialization is used for Electronic Product Code Information Services (EPCIS). This is especially important in a world in which revenue generated by counterfeit pharmaceuticals is now estimated to have reached $200 billion (1). EPCIS is an open standard that allows businesses to capture and share supply chain information about the movement and status of goods, both within their enterprise and with their business partners. Ultimately, this sharing is aimed at enabling participants in the EPCGlobal Network to gain a shared view of the disposition of EPC-bearing objects or products with serialization within a relevant business context. This EPCIS standard is essentially an advanced electronic data interchange standard specific to the bio/pharmaceutical industry.

ERP can help manage the different levels of serialization efficiently and provide users with significant benefits by simplifying the cooperation between the various players in the supply chain, ensuring compliance, and delivering transparent insights into production, logistics, and sales. By better managing these levels, bio/pharmaceutical companies will be better equipped to minimize the risks presented by counterfeit drugs.

References

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Risk-Based Approach. All of this information supports the concept that ATMPs are different and offer unique challenges regarding sterility. This recognition allows you to pursue options for demonstrating sterility including the use of rapid microbiological/sterility testing equipment.

The best way to proceed forward in getting approval for rapid techniques is to make sure you have performed the proper installation qualification/operational qualification and performance qualification on the equipment and have demonstrated its suitability for use with a complete validation package. In case there is an equipment failure, you should have backup methodologies identified as part of your quality risk management plans. The final word of advice is to make sure you and your organization have a robust, well-documented quality risk management plan that is in line with the concepts set forth in International Council for Harmonisation Q9 Quality Risk Management.

References


Q. Do I have to follow traditional pharma rules when I investigate deviations for my emerging therapy?

A. There is really no process difference when performing deviation investigations for traditional pharmaceutical products versus biotech products versus advanced therapy medicinal products (ATMPs). The purpose of performing an investigation into a deviation is to determine why the deviation happened and what its impact was on the product quality. To determine the impact of the deviation on the product quality, it is important to determine the root cause of the deviation.

The process used in the industry to determine root cause is, of course, the investigation procedure. This procedure, regardless of the type of product you are manufacturing, should require the investigator to review various systems and determine whether they were the cause of the deviation under investigation.

It is important to remember when performing an investigation to keep the following few general rules in mind:

- One size does not fit all. Simple errors require simple corrections, while serious deviations require broader investigations.
- The complexity of the investigation is related not only to the seriousness of the incident but also to the myriad of factors that could influence the outcome.
- If you follow your investigation procedure and thoroughly document your results, you should have an acceptable investigation regardless of whether you are manufacturing a traditional product or a biotech product.

The language in EudraLex Volume 4 for ATMPs (1) supports this concept by stating, “As long as the specifications for the finished product are met, a QP [Qualified Person] may confirm compliance/certify a batch where an unexpected deviation related to the manufacturing process and/or the analytical control methods has occurred provided that: (i) there is an in-depth assessment of the impact of the deviation which supports a conclusion that the occurrence does not have a negative effect on quality, safety or efficacy of the product, and (ii) the need for inclusion of the affected batch/batches in the on-going stability programme has been evaluated, where appropriate.”

Q. I need to get my product to the patient before the traditional test for sterility is concluded. This requires me to release product at risk. Is there any way to avoid this?

A. The global regulatory authorities are aware that the ATMP manufacturers face this and similar situations, and rather than have you release your product at risk, they have offered guidance that not only recognizes this situation but offers solutions to alleviate it.

The European Union states, “[a]pplication of the sterility test to the finished product (Ph. Eur. [European Pharmacopoeia] 2.6.1) may not always be possible due to the scarcity of materials available, or it may not be possible to wait for the final result before the product is released due to short shelf-life or medical need. In these cases, the strategy regarding sterility assurance has to be adapted” (1).

In a 2020 Guidance for Industry, FDA recognizes that traditional analytical methodology may not be suitable for this product category stating, “Analytical procedures different than those outlined in the USP [United States Pharmacopeia], FDA guidance, or Code of Federal Regulations (CFR) may be acceptable under IND [investigational new drug] if sponsors provide adequate information on test specificity, sensitivity, and robustness” (2). This guidance goes on to recognize the limitations of the traditional sterility test stating, “We recognize that the compendial sterility tests (USP <71>; 610.12) may not be suitable for all products (e.g., those with limited shelf life),” and “rapid sterility tests may be acceptable for ex vivo genetically modified cells administered fresh or with limited hold time between final formulation and patient administration” (2).

It should be noted that both the Ph. Eur. and the USP both recognize rapid sterility in their respective publications. Chapter 2.6.27 of Ph. Eur., titled Microbiological Examination of Cell-Based Preparations, allows for the use of automated growth-based methods or alternative methods such as a combination of direct detection by alternative methods or other methods based on the harmonized sterility test. The USP has a general Information Chapter <1071> titled Rapid Microbial Tests for Release of Sterile Short-Life Products: A
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