Conference Report

The Drug Product Track at 2017’s BioProcess International Conference and Exhibition in Boston, MA

Cheryl Scott

At the Hynes Convention Center in Boston, MA, during Knect365’s “Biotech Week Boston” in late September of 2017, one track of the BioProcess International Conference focused on drug products, fill–finish, and formulations. Presenters represented a number of major biopharmaceutical companies — AbbVie, Amgen, Biogen, Eli Lilly, Genentech (Roche), GlaxoSmithKline, Johnson & Johnson, Lonza, Pfizer, and Sanofi — as well as suppliers Bosch, Merck (MilliporeSigma), ReForm, and Single-Use Support. They focused on predictive modeling, quality by design (QbD) and process analytics, freezing–thawing and storage, endotoxin control, single-use technologies, and formulations.

Early on, James Colandene (manager of biopharmaceutical product sciences at GSK) cautioned that development and characterization of a drug-product manufacturing process should not be taken for granted. He acknowledged in his introductory remarks on Tuesday morning that most development and characterization in biopharmaceutical development centers on production of bulk drug substance (BDS). “Drug product manufacturing may be simpler than BDS manufacturing,” he pointed out, “but it’s not simple, and knowledge gaps can have significant consequences.” A company can lose entire BDS lots if something goes wrong in drug-product operations. He noted that both the BDS and drug product (DP) processes must be well characterized before process validation and commercial manufacturing.

“That’s an expectation of process design in the current three-stage approach to process validation,” he said, referring to process design, performance qualification, and continued process verification or maintenance of the validated state (according to ICH Q10). The extent of process characterization for a given unit operation may be guided by risk assessment. Basic unit operations that should be characterized include thawing of BDS, compounding and mixing, filtration and filling, lyophilization (if applicable), stopper insertion and sealing, and inspection.

Case Studies, Lessons Learned

The session began Tuesday morning with general discussions of lessons learned. Both Colandene and Shen Chen (director of PEH Pharm Sci at Pfizer CenterOne R&D) offered up multiple case studies from in-house and contract manufacturing. Chen focused on material selection; Colandene on formulation effects, components, and filling processes. They brought up a number of issues that would be explored in more depth later on the program.

Change Control: Chen highlighted regulatory guidelines emphasizing DS system control after changes to drug substance (DS). “It’s connected to laboratory testing and control and fit into manufacturing production lines, packaging and labeling, and delivery to customers. Controlling materials is the foundation of safety.” A target product profile (TPP) should guide materials considerations, and the key goals are to keep potency high and impurities low while...
maintaining regulatory compliance. All things being equal, a company would choose the most “manufacturing-friendly” options.

During product development, Chen said, the TPP can change based on clinical and regulatory feedback. Material changes are almost inevitable. And postapproval changes often come later as a means of cutting costs, dealing with supplier issues, and so on. Chen categorized three types of changes: process changes (including raw materials), equipment changes, and location/site changes.

In four case studies, she illustrated how things should go and how they can go wrong. In one outsourced project, the contract fill–finish team identified a small excursion in the drug-substance impurity profile that the client deemed insignificant. But it led to precipitation in the final formulation — deemed to be related to salt concentration and pH adjustments. A small process change solved the problem. “Based on the lesson learned here, we improved our checklist for incoming materials to add more structure analysis and study the methodologies thoroughly. It recommends batch studies for all incoming materials.”

All four of Chen’s case studies emphasized close communication and collaboration between DS and DP manufacturers, especially when they are different companies. Sometimes changes made to a DS process affect DP results — or changes can be made on one side to correct problems encountered on the other. But Colandene demonstrated how DP processes can be adjusted to handle DS issues such as high concentration, thaw-rate sensitivity, and lyophilization challenges.

In the case of a highly concentrated monoclonal antibody (MAb) formulation, filling syringe clogging was the problem. It caused variation in fill weight and low yield, and troubleshooting studies showed that the 2–8 °C storage temperature made the bulk solution too viscous. When it was allowed to equilibrate to room temperature before filling, the initial problem was solved.

Another product had been filled elsewhere for years with no problem. But transferring the same process to a new site led to clogged filters after compounding. Glycine made the formulation particularly sensitive to thaw rates — such that the only minor difference at the new site (a smaller thawing room with closer shelf spacing) made a significant change to an otherwise identical process. The surprisingly simple solution was an addition of fans to increase heat exchange in the new facility’s thawing room.

**Freeze-Dried Products:** Colandene also described how a lyophilized product showed “fogging” or product streaking on vials of final product. It was attributed to a surface-tension issue and product migration within vials during freezing. Because there was no effect on product safety, quality, or stability and it was proven to be only cosmetic in nature, cost/benefit analysis precluded making changes to the process or components. However, after many problem-free lot runs, one batch had a ~28% reject rate occur in the capping/sealing line because of raised stoppers. The problem recurred with a new lot of stoppers and vials. Stopper design was identified as the primary cause: It lacked robustness for maintaining closure, particularly when stoppers were made using worn, aging molds. In the short term, the supplier implemented new molds to solve the problem; for the long term, a stopper design change was made.

With a follow-up presentation, Shubhadra Singh (an investigator in biopharm product sciences at GSK) offered more detail. Regarding the surface-tension issue Colandene had described, with fogging during the freezing step of freeze-drying, Singh explained how such a phenomenon could be reduced through controlled ice nucleation during lyophilization. Although vials from a different supplier could lessen the instance of that cosmetic defect, she provided evidence showing how it also could be minimized by control of ice nucleation during freezing.

In classic freeze dryers, the freezing process was uncontrolled. Ice nucleation could occur at any point, with resulting differences in ice-nucleation temperature and a high degree of supercooling. If ice nucleation occurs well below zero degrees, sublimation rates are slowed by small pores in the ice, and that lengthens primary drying times — which can lead to product heterogeneity. Controlled freezing, however, lessens the degree of supercooling and creates larger pores in the frozen solution, speeding up sublimation and primary drying. Through case studies using the LyoStar3 system from SP Scientific with highly concentrated MAb formulations, Singh showed how it could improve product homogeneity based on lyophilized cake morphology, resolution of the vial fogging effect, and improved stability after exposure to shaking.

**Highly Concentrated Products:** Vineet Kumar (principal scientist in drug product development at Johnson & Johnson) elaborated further on highly concentrated formulations in “Satisfying Very High
Dose Needs of Biologics: Ultrahigh-Concentration Formulation Development, Manufacturing, and Delivery.” He defined a high-concentration formulation as one with protein >150 mg/mL and mentioned that some products in development are as high as 250–300 mg/mL — some as classic aqueous formulations, others as crystalline or oil-based suspensions. Then he described the types of manufacturing (stability, manufacturability) and delivery (safety, efficacy, and administration) complications that such high protein concentrations can bring, primarily because of their viscosity and protein–protein interactions.

The higher a solution’s concentration is, the lower the interparticle distance will be between its components. In dilute conditions, their interactions mainly are based on electrical charge. But as the distance between particles shortens and they can touch each other, less-understood forces can come into play allowing for, e.g., hydrophobic and dipolar interactions that can complicate or even supplant charge interactions. Kumar’s team screened a large number of hydrophobic excipients, amino acids, miscellaneous polyols, carbohydrates, detergents, and polymers to determine their effects on the chemistry of highly concentrated formulations. “Maybe we could find some usable, nontoxic, platform excipients that we could use going forward.”

The team did identify some leads — e.g., phenethylammonium iodide, camphorsulfonate, and certain amino-acid combinations — that brought solutions to their company’s viscosity goal of 10 cP or less (the limit for GSK’s autoinjector device). Some other companies claim that patch pumps can handle as much as 20-cP viscosity. Singh went on to discuss stability and manufacturability challenges and how different excipients might help with both.

He also pointed to technological solutions that also could contribute — e.g., single-pass tangential-flow filtration (TFF) and peristaltic pumps — as well as delivery options from companies such as West Pharmaceutical, Enable Injections, and BD Biosciences. And he described Halozyme Pharmaceutical’s Enhanze delivery technology (available for license, not as a product for sale) as a different approach for subcutaneous injection based on a recombinant enzyme. After an extensive question and answer session, the general consensus was that formulators and process developers face a “delicate dance” between concentration and viscosity, manufacturability and stability, and delivery efficiency and patient comfort.

Later in the week on Thursday, Dan Greene (senior research scientist at ReForm Biologics) introduced the idea of caffeine as an excipient for highly concentrated formulations. Proteins are notoriously sticky and prone to aggregation, which is made more likely when the interparticle spaces are reduced or eliminated in a formulation.

“Because of caffeine’s multimodal interaction with the protein surface,” he said, “we think it can be broadly applicable to many different biologics.” Greene showed that the molecule can reduce the viscosity of highly concentrated protein formulations when present at about 10–30 mg/dose, “essentially equivalent to the caffeine in a bar of chocolate.” It is already a familiar ingredient in the Excedrin painkiller, which combines it with aspirin and acetaminophen. And Greene showed encouraging data based on infliximab studies at 200 mg/mL.

“Caffeine can substantially lower the solution viscosity of highly concentrated biologics,” he concluded. “It works by physically binding protein surfaces, primarily at their positively charged residues and aromatic residues, to inhibit attractive protein–protein interactions that lead to a high viscosity at elevated protein concentrations. In vitro experiments show that caffeine does not interfere with target binding.” Every biologic is different, and formulations must be optimized for each molecule. As with any other excipient, caffeine will work for some molecules, but maybe not for others. But it is well known to regulators, which should facilitate risk evaluations toward its adoption into biotherapeutic formulations.

**Modeling and Quality By Design**

**Endotoxin Control: Risk management is increasingly important as part of the quality by design (QbD) paradigm. On Wednesday morning, Robert Simler (associate director of engineering and technology at Biogen) demonstrated its role in process control of drug-product manufacturing. His company had identified low endotoxin levels as a critical quality attribute (CQA) for an intrathecal injection product. Whereas the average endotoxin limit for most parenteral drugs is 5 EU/kg of a patient’s weight, such spinally injected products require endotoxins to fall below 0.2 EU/kg dosage. For infant patients, the limit would be even lower (0.17 EU/kg). By comparison, the limit for water for injection (WFI) is 0.25 EU/mg.

With a detection limit of 0.2 EU/kg, the final product’s endotoxin assay wasn’t validated to make...
the necessary determination. Rather than focus on a single unit operation, Simler's team assessed endotoxin risk across the entire drug product manufacturing process. That's because although each individual component might contribute a small amount, all those contributions add up in the end. This is an approach, he said, that "can be applied to any CQA that requires extremely tight control."

First they identified all potential sources of endotoxin and categorized them: raw materials (e.g., WFI, excipients, and the drug substance itself), process equipment and components (in this case, all single-use technologies), and the container–closure system at the end of the fill–finish process. To estimate the endotoxin contribution from each of those, the team referred to certificates of analysis (CoAs) and incoming goods testing performed by the drug-substance manufacturer (in this case a contract manufacturing organization, CMO) to determine the maximum possible theoretical endotoxin coming from each individual product and process component.

Doing so helped them identify high-risk areas, which included both WFI and the active pharmaceutical ingredient (API) itself. So process controls and quality-assurance measures were put in place where possible to lessen those sources of endotoxin contribution. One interesting discovery was that although the WFI specification at one CMO was 0.125 EU/mL, over a year's worth of test results had shown that the actual value never exceeded the test's limit of detection (LoD), which was 0.05 EU/mL. In fact, reviewing historical test results elucidated a number of endotoxin sources that trended much lower than their specifications would suggest.

Simler mentioned that process equipment was the most difficult thing to assess in this approach. Vendor CoAs tend to report "pass/fail" results (based on specifications) rather than actual numbers. In addition, the specifications were not always expressed in relevant or easily translatable terms. This can require some back-and-forth between user and supplier. Some vendors were more cooperative than others. "Transparency would be very beneficial to us in the future," Simler said. "It was difficult to get this information. We want to continue using a single-use system the whole way through this process, but we need to make sure our drug product won't fail because of these kind of things."

Another risk management approach is predictive and theoretical process modeling. On Tuesday afternoon, Suresh Nulu (a senior engineer in parenteral process development, also at Biogen) described how this could work for drug product manufacturing process development. He emphasized verification of models in context to gain trust in them and realize their usefulness. "It's about how to make data-driven decisions."

Prior knowledge assessment, as Simler also described, can be an important part of this. Good models are built on accurate data.

Such models can inform process development decision-making. Instead of doing a design of experiment (DoE) based on 15 data points, for example, you can study only three, verifying them with a trustworthy model, and save time and resources. "That's how we are going to deliver our medicine to the patients faster," Nulu said, "also more economically and with better quality." He presented some mixing and lyophilization case study data to illustrate his point.

Mark Palmer (PPE device engineering scientific leader in R&D platform technology and science at GlaxoSmithKline) followed with a more extensive case study of product filling. "We had a problem with some drying-out of filling needles causing blockage. And we've seen this reported in the literature. It's driven by the need to go to higher concentrations." The product in this case was a 200 mg/mL formulation.

When a filling line is stopped, each needle will be tipped with a droplet of drug product in an environment that is conducive to drying. Highly concentrated formulations have less moisture and thus dry out more quickly. The filling needles can become blocked. In most filling processes, peristaltic pumps can be reversed slightly to suck the product back just enough to prevent this problem by creating a meniscus (crescent-shaped) surface on the liquid within the filling needle — away from drying airflow. Physical modeling of that process helps developers determine exactly the amount of pump pressure to use, the optimum diameter and material for tubing and filling needles, and so on.

**Process Monitoring:** Accurate data form the basis of good modeling and decision-making. At the end of the day on Tuesday, Edwin Vilanova Velez (finished-goods MSAT engineer at Genentech, a member of the Roche group) and Evan Justason (CEO of Smart Skin Technologies) presented an example of filling-line pressure
distribution. They described how the latter company’s QuantiFeel line-monitoring drones (vial “clones” placed in line with the real thing) can replace visual inspection to provide real-time sidewall pressure data during filling processes. This type of monitoring provides information that can help companies prevent glass breakage, defects, and filling interruptions. Using such online pressure measurements, Genentech was able to optimize its filling, inspection, and packaging lines to protect vial integrity. The supplier is currently working with a development partner to expand its system’s use from vials to prefilled syringes and cartridges.

**Technological Innovations**

Wednesday’s presentations took up where Tuesday left off with a focus on other new innovations — particularly in freezing, storage, and thawing technologies. As everywhere else in bioprocessing, disposables are playing an increasingly important role in drug-product manufacturing.

**Single-Use Filling Technologies:** Bosch product manager Dena Flamm offered general considerations for implementing disposable filling systems in a sponsored presentation that also featured Sarah Bell (head of technology management at MilliporeSigma). Their two companies have partnered to offer PreVAS rolling-diaphragm systems: prevalidated, preassembled (in a class 10,000 cleanroom) custom assemblies that are presterilized with gamma irradiation to make them ready for use.

After Flamm listed benefits of single-use filling technologies — shortened change-over times, capabilities for small batch sizes (e.g., personalized medicine), elimination of cleaning and associated validation concerns, and deferred capital investment for clinical-stage products — Bell went on to suggest best-practice considerations. “First and foremost,” she cautioned, “do your homework.” Developers need to understand how compatible their products are with polymeric materials before choosing to implement single-use technologies. They need to define their own particular use requirements (e.g., assembly design, quality needs) and then find the right supplier, “someone to collaborate and partner with to give you what you need, from additional design expertise and knowledge of single-use technologies to robust quality systems, which are especially important for a critical application like final filling.”

Bell also emphasized testing to ensure that equipment is fit for its intended use — again, a collaborative process among users and all involved suppliers (e.g., in this case Bosch and MilliporeSigma). That partnership approach should continue through factory-acceptance testing (FAT) and engineering runs, as well. Finally, she highlighted the importance of training: “It’s not a very easy transition from stainless steel to plastic components. You need to educate the people working with these systems in the warehouse, transportation, installation, and manufacturing to make sure that they have a clear understanding of how to handle them according to clear and consistent standard operating procedures (SOPs).” That advice also applies to equipment for freezing, thawing, and storage. This was the topic of the Wednesday morning session featuring talks by Mark Yang (director of global biologics development at Sanofi), Jeffrey Johnson (new technology lead at Merck), Johannes Kirchmair (managing director at Single-Use Support), and Kapil Gupta (associate director of protein pharmaceutical development at Biogen). Bulk drug substance often is frozen before it goes into formulation as a drug product, usually for logistical reasons such as protection during transportation and extension of shelf life. Even during drug-substance manufacturing, process intermediates may go through a freeze and thaw when downstream purification timing requirements demand it.

“Bulk freezing can be very stressful to proteins,” Yang cautioned. Sources of stress include interactions with container–closure surfaces, cryoconcentration effects, pH shifts, and stabilizer loss or crystallization over time. He pointed to a number of available technologies for mitigating these stresses. And as one audience member pointed out, thawing can present its own challenges (e.g., osmotic shock). Harkening back to a Tuesday presentation by GSK’s Shubhadra Singh, the discussion centered here on process control.

Johnson identified benefits and problems on different options, from controlled freezing and thawing systems to single-use bags to stainless steel cryosystems. “So we set out about five years ago with a mission of developing a robust, scalable, cost-effective platform to manage drug-substance freezing that ensures stability during freezing, storage, shipping, thawing, and processing.” He went on to describe the platform his team developed based on single-use containers. “We have an agreement with Meissner Filtration
Products to market this product, which they hope to launch at Interphex in 2018.” In a lively question-and-answer period, one audience member compared the presented results favorably with another commonly used freeze–thaw system.

Kirchmair went on to describe his supplier-company’s approach to what he called “bulkstream management.” The industry trend toward single-use technologies in these logistics matters is clear. And perhaps the most common complaint regarding disposable bags is that they leak. Kirchmair’s company provides support systems (handling 250-mL to 300-L volumes) to help prevent that from happening. “We take the bag that the customer uses already and put it in a shell that truly protects it. You can drop it on the floor in a frozen state at –70 °C, and nothing will happen to the bag at all.

“But nobody wants to drop bags. Nobody wants to pay for manual manipulation, and nobody wants to train more people than necessary. So as little manipulation as possible should be part of a typical bulkstream bag-handling process.” He explained that SOPs can be designed around this desired hands-off state.

Lyophilized Drug Substance: Finally, Gupta highlighted an alternative to traditional freezing: spray freezing and dynamic freeze-drying with Meridion Technologies SprayCon and LyoMotion systems. “Cold chain is a good safety net,” he said. “But it does provide logistical challenges, especially when you’re thinking about a global manufacturing network with drug substance on one side and drug products on multiple other sides. Just shipping around high-volume, frozen materials across the continents poses a tremendous challenge, from the limitations of dry ice on cargo planes to pressure excursions and scalability.” Biogen wanted a way to address those issues, and Meridion technology offered a solution.

Spray drying is a continuous process that is already well established for small molecules, but it can be difficult for temperature-sensitive biologics. SprayCon technology creates frozen microspheres, and LyoMotion systems introduce lyophilization to the process. The output is an easy-to-handle, free-flowing drug-substance powder that is room-temperature stable and can be reconstituted and formulated as a drug product. Biogen tested the systems with a MAb product with good results.

This might have disruptive potential. Gupta imagined a future where the drug-substance powder could be the final product, itself — with pharmacists performing the compounding at the point of use, as is the case with some oral medications. “Obviously there are challenges with any new technology. This is not a plug-and-play lyophilizer that you just bring in. The tower has a fixed height of 40 feet, which must be considered early in facility design — as does packaging to maintain properties of the powder (sterility and moisture) and validation of sterility.

Protecting the Final Product
In the foreseeable future, biologic products will continue to be formulated, filled, and finished in familiar ways. And those final results are likely to be parenteral products, whether they are packaged in vials, ampules, prefilled syringes, or cartridges. And the kinds of issues that these products can encounter at their point of use suggest that a direct line from drug substance to patient wouldn’t be a necessarily straightforward path.

That was an underlying message in Wednesday afternoon’s discussions, which began with presentations on particles and light exposure from Ganapathy Gopalrathnam (principal research scientist at Eli Lilly and Company) and Vivek Kumar Garripelli (senior scientist in biologics formulation development at AbbVie), then concluded with a panel discussion on mitigation strategies for drug-product technical challenges. See below for more discussion.

Aggregates and Particles: Early on Tuesday, another presenter had introduced concerns about closed-system transfer devices (CSTDs) for MAb preparations. Those of us who have had intravenous drug-infusion treatments (e.g., chemotherapy for cancer) have seen our nurses use such devices to hook up their patients to IV bags. CSTDs mechanically prohibit both the transfer of environmental contaminants into a system and the escape of hazardous drug or vapor concentrations outside it. Since first appearing on the market in 1997, these devices have become a regulatory recommendation. The photo on page 3 shows one.

As the speaker explained, the many CSTD systems on the market are made from a range of materials: e.g., silicone polymers, polyesters, polyethylenes, polycarbonates, acrylonitrile butadiene styrenes, and stainless steel. After testing different models and needle-free related devices with a MAb formulation, her team found highly variable results. Some devices introduce silicone oil droplets into transferred fluids, for example, and others release protein-degrading
Finding the Recipe — Formulation Strategy Discussion

For many people working on drug-product manufacturing, formulation is just a recipe. Like expert chefs, they mix the drug substance with precise amounts of several other ingredients — in the right order, under the right conditions — and prepare the final product for delivery to clinics and pharmacies. But they depend on precise determinations of how best to protect and deliver the drug substance in product form. And the chemists who make those decisions once had a reputation in the industry that bordered on magical.

But as with every other aspect of biopharmaceutical development, quality by design (QbD) has transformed the work of formulations. As Benson Gikanga (pharmaceutical processing and technology development engineer for Genentech) pointed out on Thursday morning, QbD can simplify a formulator’s job. He pointed to three important considerations: product/process knowledge; scientific and engineering concepts (including equipment and instrumentation); and modeling and risk assessment. In an example case study, he described how his team chose among available mixing technologies.

Other case studies came from Sekhar Kanapuram (director of drug product technologies at Amgen) and Frédéric Mathot (senior scientist in drug product R&D at GlaxoSmithKline Vaccines). Kanapuram reported on development of a low-dose drug product and Mathot on a live adenoviral Ebola vaccine.

For the latter product, temperature was of primary concern. Because it was intended for use at various types of clinics in Africa, the vaccine had to be stable at both freezer and refrigerator temperatures — and it needed to be filled in ≥20,000-vial lots. During its very rapid development, GSK had to find/create and implement process analytical tools and knowledge. The company went with a lyophilization strategy and PAT based on dynamic light scattering (DLS) and fluorescent staining for physicochemical integrity, quantitative polymerase chain reaction (qPCR) for virus particle quantification, and fluorescence-activated cell sorting and infectivity assays. A stable vaccine formulation came from work conducted on both the lyophilization matrix and the cycle itself. “Synergistic effects of both aspects cannot be neglected,” he cautioned, “when an optimized freeze-dried formulation is desired.”

Arvind Srivastava (research advisor in formulation development at Eli Lilly and Company) also focused on thermal stability. Temperature excursions — when a drug product is exposed to heat or cold outside its specifications, often during shipping and distribution — can lead to revenue losses and supply chain interruptions. Proteins can unfold or crystallize when they get too cold; they can unfold, aggregate, precipitate, and form particles when they get too hot. Chemical reactions are accelerated by heat, as well. But as Srivastava pointed out, the length of time that an excursion lasts makes as much a difference as the temperature itself: A week at a slightly higher than optimal temperature can be worse than a few seconds of extreme heat.

For determining a product’s true limitations, Srivastava recommended cycling studies during stability testing meant to establish its shelf life. The parameter measured is mean kinetic temperature (MKT), a simplified way of expressing the overall effect of temperature fluctuations during storage or transit of perishable goods.

Information gained from these tests can help formulators make solid recommendations regarding shipping and logistics — and adjust the recipe where necessary.

Garripelli also addressed particulate formation during product end use, focusing his talk on subvisible/submicron particles. He offered a case study of a reconstituted lyophilized product that showed different particle profiles at different point-of-use sites. His team found that one site did not store the product upright, which allowed silicone oil from the vial stoppers to come loose onto dislodged lyophilized cakes. In some cases, the oil might not interfere with product stability or quality; in others, such findings would lead to a change from silicone-oil to siliconized stoppers.

Another case study tested monoclonal, bispecific, and antibody–drug conjugate formulations for submicron particle formation with mild agitation in end-use conditions. Of the three products, the bispecific antibody was most sensitive and susceptible to aggregation. Although Garripelli mentioned that some end-use filters have been shown to release particles into IV product infusions, he showed that that was not the case here. The subvisible/submicron particles that were detected turned out to be proteinaceous in nature.
“Several factors can affect particulate formation during end use,” he concluded, citing among them protein modality and stability, dose-solution composition, and dose administration practices. “It’s not just visible or subvisible particulates that you could expect. You could start seeing submicron particles as well. The impact of those on patients (e.g., immunogenicity) needs to be explored. It’s an evolving topic.” Both the AbbVie and Genentech teams had relied heavily on Protein Simple’s microflow imaging (MFI) analysis for their work, which suggests that it has an important part to play in future discussions.

**Exposure:** Both visible and ultraviolet light also can affect product quality at the point of use — and during manufacturing. Although the former is difficult for drug makers to control, the latter deserves attention (and perhaps more so because of that). Gopalrathnam illustrated this point with data and described some control strategies that drug-product manufacturers can apply. Once testing has elucidated a given product’s nominal light exposure levels, decisions can be made about how to protect it.

“The UV component is critical in overall light exposure,” he pointed out. “If you see some aggregation, 90% of your degradation is coming from UV.” Some companies use amber glass vials/ampules to protect their drugs from UV radiation (which brings concerns with the iron oxides used to color the glass); some use light filtering during processing. Secondary packaging also helps with final products. During questions and answers, the point came up that here again (as in Simler’s endotoxin talk) is another case of cumulative exposure being a concern.

Light and shaking are far from the only stressors drug products experience in transit. See the “Finding the Recipe” box on the previous page for discussion of temperature exposure and strategies for preventing excursions and/or protecting drug products from them. The final day focused exclusively on formulations.

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**FURTHER READING FROM THE BPI ARCHIVES AS WWW.BIOPROCESSINTL.COM**

Walles D. Serialization: Background, Justification, Requirements, Timelines, and Readiness Across the Supply Chain. BPI December 2017

Maggio E. Polysorbates, Biotherapeutics, and Anaphylaxis: A Review. BPI September 2017


DePalma A. Biopharmaceutical Fill and Finish: Technical and Operating Challenges for the Latest Formulations and Devices. BPI January 2017

Scott C, Guldager N, Anderson KV. Single-Use Fill and Finish: An Interview with NNE Pharmaplan. BPI January 2017 (supplement)

Lee B, et al. Response to the Publication of USP ‹1207›. BPI January 2017


King J. Validation of Controlled Freezing and Thawing: A 9-L Bottle Study. BPI October 2016


King J. Validation of Controlled Freezing and Thawing Rates: A 16-L-Bag Study. BPI May 2016 (supplement)

Kovarčík DP. Critical Factors for Fill–Finish Manufacturing of Biologics. BPI May 2016


Maggio E. Alkyl Mono- and Diglucosides: Highly Effective, Nonionic Surfactant Replacements for Polysorbates in Biotherapeutics — a Review. BPI March 2016

Rios M. Outsourced Stability Testing: Discussions with Contract Laboratories. BPI November 2015 (supplement)


Rodríguez-Mendieta I. Biophysical Analysis: A Paradigm Shift in the Characterization of Protein-Based Biological Products. BPI September 2015


Scott C. New Approaches to Fill and Finish: A BPI Theater Roundtable at Interphex 2015. BPI August 2015 (supplement)


Hutchinson N, Bird P. Automation of a Single-Use Final Bulk Filtration Step: Enhancing Operational Flexibility and Facilitating Compliant, Right–First-Time Manufacturing. BPI March 2015 (supplement)


Castleman L. Simulating Seal Life with Finite-Element Analysis. BPI February 2015
Technical mitigation strategies were the general topic of Wednesday’s end-of-day panel discussion with Gopalrathnam, Maloney, Greene, and Sekhar Kanapuram (director of drug product technologies at Amgen). Every drug substance will present its own set of stability and shelf-life challenges as a drug product. With companies increasingly seeking to speed their products to market, it can be difficult for drug-product groups to answer all necessary questions in time for product launch. Whereas in the late 20th century it was normal for biopharmaceuticals to take well over a decade to go from concept to launch, now they are expected to go to market (assuming approval) in half as long. Consensus was that the best path for each drug substance through the obstacle course of safety, efficacy, quality, and stability to that final goal of bringing patients the best medicines possible.

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It’s No Easy Matter

GSK’s Colandene wasn’t kidding when he cautioned that biopharmaceutical drug-product development isn’t simple. All the aspects of biological drug-substance molecules that make downstream processing difficult will come into play for formulation, fill–finish, transportation, storage, and administration. It’s not just a matter of “add buffer and stir” — and even if it were, your choice of buffer, method of containment, and fluid dynamics would complicate the matter anyway. As the presenters in Boston last fall showed, technological innovations and rational scientific approaches are helping product developers choose the best path for each drug substance through the obstacle course of safety, efficacy, quality, and stability to that final goal of bringing patients the best medicines possible.

Further Reading from the BPI Archives as www.bioprocessintl.com

Straka A. Sterilization Effects on Elastomer Characteristics and Functionality in Parenteral Delivery Systems. BPI November 2014
Mattschka J, Santa-Maria V. A Critical Mission: Clinical Trial Material Storage and Distribution. BPI September 2014
Kling J. Highly Concentrated Protein Formulations: Finding Solutions for the Next Generation of Parenteral Biologics. BPI May 2014
Zambaux J-P, Barry J. Development of a Single-Use Filling Needle. BPI May 2014 (supplement)
Steele A, Arias J. Accounting for the Donnan Effect in Diafiltration Optimization for High-Concentration UFDF Applications. BPI January 2014
Briet J, DuBoise D. Spray-Dry Manufacture of Vaccine Formulations. October 2013 (supplement)
Maggio E. Biosimilars, Oxidative Damage, and Unwanted Immunogenicity. BPI June 2013
Mire-Sluis A. Drug Products for Biological Medicines. BPI April and June 2013
Kling J. PEGylation of Biologics. BPI March 2013
Perkins M. Tunable Half-Life Technology. BPI March 2013
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