APIs, EXCIPIENTS, & MANUFACTURING 2018
Right on target.

Capsugel®

Vcaps® Enteric capsules

The intrinsically enteric capsule

No coating needed

More than 9 months of development time saved

High API protection

Made better. By science.

Want to know more?
Visit www.capsugel.com
service representative will assist you in removing your name from UBM America’s lists. Outside simply call toll-free 866.529.2922 between the hours of 7:30 a.m. and 5 p.m. CST and a customer
America’s to make your contact information available to third parties for marketing purposes, products, services, and other opportunities that may be of interest to you. If you do not want UBM phone numbers, and e-mail addresses) to third parties who wish to promote relevant prod-
the advertisements contained in the publication, and cannot take responsibility for any losses or
other damages incurred by readers in reliance of such content.

UBM Americas provides certain customer contact data (such as customers name, addresses, phone numbers, and e-mail addresses) to third parties who wish to promote relevant prod-
ucts, services, and other opportunities that may be of interest to you. If you do not want UBM America’s to make your contact information available to third parties for marketing purposes, simply call toll-free 866.529.2922 between the hours of 7:30 a.m. and 5 p.m. CST and a customer service representative will assist you in removing your name from UBM America’s lists. Outside the US, please phone 218.740.6477.

Pharmaceutical Technology does not verify any claims or other information appearing in any of
the advertisements contained in the publication, and cannot take responsibility for any losses or other damages incurred by readers in reliance of such content.

Pharmaceutical Technology welcomes unsolicited articles, manuscripts, photographs, illustrations, and other materials but cannot be held responsible for their safekeeping or return.

Single issues, back issues: Call toll-free 800.598.6008. Outside the US call 218.740.6477. Licensing and Reuse of Content: Contact our official partner, Wright’s Media, about available usages, license fees, and award seal artwork at Advanstar@wrightsmedia.com for more information. Please note that Wright’s Media is the only authorized company that we’ve partnered with for Advanstar UBM materials. Display, Web, Classified, and Recruitment Advertising: Contact, Tel. 732.596.0276, Fax 732.647.1235

MANUFACTURING 2018

API IN CAPSULE

s4 Application of API-in-Capsule
Best Practices to Accelerate Drug Product Development

Jeff Williamson

CGMP EXCIPIENT AUDITS

s8 Third-Party Audits: Ensuring That Excipients Meet cGMP Requirements

David B. Klug, Ralph D. Lindblad, Douglas G. Muse, Katherine L. Ulman, Phyllis Walsh, and Priscilla S. Zawislak

EXCIPIENTS

s14 Paving the Way for Modernized Drug-Product Manufacturing Through Excipients

Amina Faham, Kathryn Hewlett, and True Rogers

ANTIBODY-DRUG CONJUGATES

s18 Tackling Aggregation Challenges in ADC Production

Adeline Siew

ASEPTIC FILLING

s20 Robotics Solve Aseptic Filling Challenges

Jennifer Markarian

TOPICAL DELIVERY

s22 A Perspective on the Topical Delivery of Macromolecules

Jennifer Markarian

QUALITY CONTROL

s26 Ensuring Consistency in Content Uniformity Testing

Agnes Shanley

SPECIAL SECTION

CPhl 1 CPhl Worldwide 2018 Planning Guide

CPhl 12 Ad Index

On the Cover: Bukhta Yurii/Shutterstock.com/Dan Ward
Pharmaceutical companies are faced with the routine challenge of screening and advancing their active pharmaceutical ingredients (APIs) through a drug product lifecycle. Early investments in the APIs are often costly. Identifying viable candidates for clinical dosage early and eliminating less viable or non-viable candidates are, therefore, crucial in meeting aggressive project timelines. These new APIs have key risk areas that dictate understanding of physicochemical properties when the synthesis process is in early stages. Physical and environmental effects can define these compounds as “challenging” as they move from drug substance manufacturing into drug product development, and therefore, they require additional processing steps or control measures to promote the API into a viable dosage form. Environmental effects such as hygroscopicity, light sensitivity, and the need for containment can pose some initial risks as the API is introduced into the development pathway.

Specific processing steps, specialized capsules, and micro-dosing encapsulation techniques are available to address and mitigate environmental and physicochemical challenges, streamline development processes, and accelerate clinical timelines. Precision powder micro-dosing systems facilitate the rapid manufacture of API-in-capsule (AIC) drug products that can be expediently dosed in oral or pulmonary administration routes. These AIC dosage form presentations can reduce API consumption and early-stage evaluation time (Phase I and II) by eliminating the need for specific formulation steps, such as excipient compatibility testing. AIC studies have become a beneficial evaluation technique for highly potent, low-dose applications where accurate micro-dosing is required.

Preformulation: Setting the tone for drug products

Drug substance manufacturers have an exhaustive list of challenges in synthesizing new compounds to bring forth the purest, most stable candidate. Addressing issues such as “lot-to-lot variability” and “scale factor” can be a daunting task for product development teams as they start down the
path of evaluating and advancing candidate compounds. Although mitigated by experimental designs, APIs may gain more defined physical risk factors, such as changes in particle size and flow properties, as they progress through the development process, which can have a profound effect on how the dosage form will be developed.

A significant number of steps go into both API synthesis and drug product development, and a full understanding of the API characterization is a crucial starting point. It is never too early to investigate physicochemical properties of new compounds, and the data from initial screening is the source for a number of debates between synthesis chemists and drug product development teams. These initial discussions and data should take into consideration the dosing range, potency, hygroscopicity, solubility, flow properties, moisture/light/oxygen sensitivity, and other physicochemical assessments that can affect drug product design and development. Preformulation typically entails x-ray powder diffraction to detect polymorphs, pH solubility profiling, understanding of hygroscopicity through vapor sorption analyses, and particle morphology by scanning electron microscopy and sizing through laser diffraction, allowing design teams to determine if the API is crystalline or amorphous with good or poor flow characteristics. At this stage, product development teams have more information to define the initial target product profile and are challenged with defining an expedient path to a final dosage form. To expedite the program, the API could potentially be introduced into an accelerated pathway by dispensing it solely into a capsule for dosing while other conventional development action steps are in planning stages.

**API in capsule: Micro-dosing systems and approach**

Micro-dosing can prove essential for accelerating drug product development and quickly introducing a dosage form into various clinical phases. Micro-dosing is essentially the precision weighing and dispensing of powders into capsules using various equipment platforms or techniques. Micro-dosing has become more prevalent with the rising number of highly potent candidate compounds for oncology and other indications.

APIs (or blends and other formulations) may be directly encapsulated to accelerate the identification of viable prototypes and move them expediently into clinical studies. Depending on the material physical attributes, API doses as low as 100 micrograms can be encapsulated with minimal variance in weight. In a typical drug product project plan, there are demands on API quantities for analytical method development efforts, excipient compatibility studies, and initial experimental evaluations of formulation and process. API availability can be quite limited in these early stages of evaluation and screening, so an efficient AIC approach can prove crucial in providing a “jump start” to dosage form development, eliminating the need for excipient compatibility studies, and minimizing the usage of APIs. For blends and other formulations, some adjustments may be required in a development program for dose ranging studies. Depending on the physical properties of the powder blends, micro-dosing may be used to provide multiple strengths using the same formulation.

The neat API or a powder blend can be encapsulated, used for analytical assessments, and even placed on stability studies while other approaches of drug product development are conducted in parallel or in sequence to support a particular program. More importantly, if the program requires multiple strengths for preclinical or clinical dosing, an AIC approach provides the ability to dispense the powders using exactly the same precision weighing process.

Xcelodose Precision Powder Micro-Dosing Systems (Lonza) have been widely adopted for early phase AIC studies. Figure 1 depicts the operating principles for this technology where powder is dispensed through a mesh screen at the base of a dispense head based on precise tapping technology. Powder is released through the screen by the tapping action of a solenoid on the dispense arm that cradles the dispense head. Parameters defining the tapping process can be tightly controlled and include dispense head type, mesh hole size, number of holes, tapping frequency, and desired dispense rate. These parameters are selected based on the physical characteristics of the material and desired dose.

The system accurately controls capsule dosing by continuously monitoring the net weight being dispensed in real-time and automatically adjusting the tapping rate during dispensing. As the weight approaches the target value, the rate of powder delivery is reduced and then eventually stopped when in the fill weight range. Once the dispensing operation is complete, the systems have the ability to recognize and reject units that are under or over weight based on the predetermined fill weight range. These systems also provide comprehensive documentation for the filling operation, including individual weights of each capsule produced in the run.

**Micro-dosing: Capsule selection**

Once the initial preformulation assessments of the API have been performed, and the route of administration is
Confirmed, decisions can be made for the capsule composition and size. Most of the capsule presentations used for micro-dosing range from Size 4 up to Size 00. Particle size, powder densities, and any necessary salt correction factors further define the size of capsules, while hygroscopicity, chemical structure, and stability of the compounds may define the capsule composition. There are a wide range of capsule presentations available for use in micro-dosing, geared to accelerating drug product development. The conventional approach has been using gelatin capsule shells; however, there are other encapsulation options when formulators are faced with challenges, such as moisture-sensitive APIs or having to encapsulate or store under lower humidity conditions.

Alternative polymers have been introduced into capsules for several technical and market reasons, for example, to better avoid unwanted impurities due to moisture ingress with hygroscopic APIs and to avoid brittleness from conventional gelatin capsule shells. Hypromellose and hydroxypropylmethylcellulose (HPMC) capsules (e.g., Capsugel VCaps Plus) have evolved to give drug product formulators more flexibility and stability beyond gelatin presentations—they contain less water, eliminate moisture-driven impurity concerns from the shells, and can withstand lower humidity conditions for encapsulation. Capsules have been used as part of pulmonary delivery devices, which have specific requirements that influence product design, especially because very small amounts of APIs or blends are introduced into them. HPMC capsules are, therefore, typically the preferred capsule for dry powder inhalation (DPI) applications due to efficient capsule clearance upon actuation in DPI devices.

Not all APIs are intended for immediate release for performance reasons, such as likely instability in acidic conditions or projection of improved absorption rate further in the gastrointestinal tract. Early formulation and process development of enteric delivery or delayed release dosage forms can add significant development time due to the required coating steps to achieve this functionality. Capsules have been engineered with suitable enteric polymers (e.g., Vcaps Enteric) in the actual shell composition, allowing delayed release or enteric protection of the contents without having to employ time-consuming coating processes. These intrinsically enteric capsules can be readily used in AIC approaches for preclinical and clinical assessments.

**Case studies of micro-dosing applications**

**High-potency API (HPAPI).** In a representative case study, the challenge presented was an HPAPI, low-dose application for initial clinical presentation on an aggressive timeline. The target dose for the clinical program was 0.1-mg fill weight into a size 1 capsule. Several fill evaluations were performed under containment to determine the appropriate dispensing head, tapping frequency, and other parameters for a reasonable yield. Through early experimental evaluations, the parameters were identified to produce capsules on the small-scale Xcelodose 120S and transferred to the higher capacity Xcelodose 600S for GMP production. The yield for this operation was only 46%, which was expected as the fill weight was exceptionally low, though overage was produced to meet the desired quantity with minimal loss of API. The clinical delivery date (i.e., overall program from preliminary evaluations to clinical release dosage form in three months) was met.

**Blends.** Micro-dosing is not only geared toward neat API, though this is certainly the primary application. The technique is also used to introduce blends into capsules when necessary. Using this approach can be tricky because the tapping mechanics and gravity fill can introduce blend segregation, leaving analytical teams chasing a content uniformity issue during testing. In a representative case study, the challenge presented was to provide a pediatric dose of 5 mg using a current formulated capsule of 30 mg strength with a lower fill weight initially. Once again, the timeline challenges of this “one-time” batch did not warrant re-formulation and additional stability studies. Using Xcelodose technology, the capsules were produced and tested to ensure uniformity of dosage unit to meet the clinical delivery date. The additional reformulated pediatric capsule development timeline was reduced by an estimated four to six months.

In an additional and more challenging “API blend” case study, a comparator study was to be conducted with a commercially available immediate release tablet versus a new API. The problem was that the tablets were a much higher strength than what was needed. To address the need, tablets were actually milled to create a powder blend and filled using an Xcelodose system to the desired strength. The capsules met acceptance criteria for assay and content uniformity and progressed to the clinical dosing.

**DPI applications.** Micro-dosing can be used for DPI programs as well, as previously mentioned. Particle sizing is typically key for a DPI delivery system, and specialized DPI capsules are often employed to provide optimized capsule clearance.
Particle engineering is typically required for DPI applications to ensure an average particle size in the 2.5–3 micron range and a tight particle size distribution. Spray drying is increasingly being used to achieve the required particle size distribution and morphology for effective DPI therapeutic effect. Employing encapsulation of spray-dried API using micro-dosing can rapidly advance dosage form development, using the same filling principles across multiple dosing ranges (see Figure 2).

Scale-up considerations. A number of technological advancements have been made with micro-dosing applications at commercial scale, which facilitate efficient late-stage clinical and/or commercial scale up. Harro Höfliger, for example, has developed high-speed capabilities that are able to produce much larger quantities to support late-stage clinical and even potential commercial endeavours. The equipment has a different approach than the Xcelodose gravity-fed system but can be readily scaled from Xcelodose-based Phase I–II studies. Such systems allow for rapid-to-market approaches leveraging precision micro-dosing technology for encapsulated API or blends.

Harro fully automated devices can micro-dose powders using dosators and vacuum drums depending on the fill weight of the capsules. The dosator change parts dispense powders from 5 mg or more into capsule shells, while vacuum and membrane presentations can dispense powders into capsules as low as 0.5mmg/unit. Specifically, the Harro Modu-C MS drum filler uses custom designed drums with precision drilled holes and vacuum systems to produce low-impact forces and powders to introduce them into capsules at high rates of speed. These advancements have resulted in the ability to produce up to 72,000 capsules per hour based on the technology and powder properties. Not only is application speed increased, the quality of the micro-dosing is maintained by a 100% in-line fill mass monitoring and rejection, thus facilitating an overall rapid commercialization for AIC applications.

Summary
Using AIC approaches, pharmaceutical companies have the ability to increase speed to clinic, quickly assess their new assets, and remain cost conscious to investments in development of formulated dosage forms. AIC studies start with API characterization, from which an understanding of the API morphology, solubility, and other key attributes define the drug product design and decision flow diagram. Choosing the right capsule composition and size, employing micro-dosing encapsulation techniques, and leveraging scale-up best practices can help progress these new APIs quickly from concept to the later stage clinical/commercial drug products. PT

---

ADVANCING THE SCIENCE OF CONTAMINATION CONTROL

STERIS Life Sciences is a trusted partner and global leader in the fields of VALIDATED CLEANING, MICROBIAL CONTROL, & STERILIZATION.
To optimize your cleaning, and minimize risks to your processes, contact us.

www.sterislifesciences.com
lifesciences@steris.com l (800) 444-9009
In today’s regulatory environment, and with the importance of delivering quality medicines to patients, regulators continue to place even more responsibility on pharmaceutical companies. Although more companies are outsourcing manufacturing, it remains their job to ensure that raw materials used in their medicines, including excipients, are safe, of high-quality, and sourced from reputable suppliers who adopt appropriate manufacturing practices. In turn, excipient suppliers face a growing number of on-site audits and related information requests to ensure that their facilities and products meet the expectations of their customers (pharmaceutical companies) and regulators (1). The burden placed on audit teams at both suppliers and pharmaceutical companies is daunting.

Current audit burden facing pharma
With the introduction of the Falsified Medicines Directive (FMD) (2) in Europe and the Food and Drug Administration Safety and Innovation Act (FDASIA) (3) in the United States, regulators have made clear that the buck stops with pharmaceutical marketing authorization holders. It is their responsibility to verify that current good manufacturing practices (cGMP), ascertained from a formalized risk assessment of the excipient and its intended use, are documented and in place for excipients used in drug products. To meet this expectation, pharmaceutical companies are emphasizing on-site supplier audits and relying less on information provided from paper audits or questionnaires filled out by suppliers. For decades, pharmaceutical companies have audited some of their excipient suppliers, but the audits typically took place every three-to-five years, and each one typically required only one day to complete. As cGMP requirements for excipients have become more stringent, it can be difficult to audit even the smallest excipient suppliers in one day, at least in any comprehensive way. What has typically happened is that audits have been rushed and compromised.

In response, pharmaceutical companies have increased requests for more and longer (i.e., one-to-two-day) on-site audits. The problem with on-site supplier audits is that they

Increasingly stringent audit requirements will make third-party accredited GMP audits critical for pharmaceutical excipients and raw materials.
PARENTERAL CDMO

Grifols guides pharmaceutical companies through the process of switching from concentrated formula to pre-mixed solution in ready-to-use flexible bags.

Visit us at:
- Contract Pharma
  September 27th - 28th
  Hyatt Regency New Brunswick, NJ
- CPhI Worldwide
  October 9th - 11th
  IFEMA, Feria de Madrid, Madrid
  Booth 3F102

Contact us:
partnership@grifols.com
www.partnership.grifols.com

Still struggling to find a CDMO that fits?

GRIFOLS
are costly, both to the company performing the audit and the supplier that is being audited. For pharmaceutical companies, audits require spending on travel and accommodations for the auditing team, plus hourly rate for any contract auditors they hire. They must also budget for writing the audit report and follow up work.

Suppliers often reject requests for audits due to resource constraints and because pharmaceutical customers are not their core markets and the sales value of their business is too low to justify the time required for the audit. Based on business case and customer priority, excipient suppliers have historically hosted limited on-site audits from pharmaceutical companies. However, many excipient suppliers have hundreds or even thousands of customers and find it physically and economically impossible to host on-site audits for all of them. In addition, not all pharmaceutical company auditors are sufficiently trained in excipient GMPs, adding layers of complexity and burden to the excipient supplier.

Based on the growing need for verified excipient quality and safety information and to help alleviate the audit burden, pharmaceutical companies, excipient suppliers, and other pharmaceutical industry stakeholders have joined together to develop voluntary excipient cGMP consensus standards (4,5). These voluntary standards facilitate the use of third-party qualified auditors who have been specifically trained to audit excipient manufacturing facilities to ensure their compliance with both cGMP and current good distribution (cGDP) practices.

Recognized consensus standards and auditing programs

Today, there are two voluntary consensus standards and auditing programs designed to assess excipient GMPs (6):

- The EXCiPACT certification scheme (7), certified against EXCiPACT cGMP and good distribution standards (5), which are published as an annex to the International Organization for Standardization (ISO) 9001:2015 Quality Systems standard. The EXCiPACT certification scheme was launched in 2012 and includes the GMP and good distribution practice (GDP) for excipients as an annex of ISO-9001, the competency of the auditors, and the independence of the certification bodies as an annex of the ISO-17021.

- The NSF Health Sciences Excipient Certification Program (NSF-ECP), which certifies against the NSF/IPEC/ANSI 363: Good Manufacturing Practices (GMP) for Pharmaceutical Excipients standard. The program was launched in March 2015 and may be used by all excipient manufacturers, regardless of ISO 9001 certification status. The program is accredited by the American National Standards Institute (ANSI) and operated with oversight of NSF Corporate Quality and Compliance. The purpose of these certification programs is to apply a consistent approach to inspecting and auditing excipient suppliers for conformance to appropriate excipient cGMPs. In addition, these independent, high quality, third-party certification programs include the use of credible certification bodies (CBs) who employ qualified auditors who have been shown to be competent in the related standards, to issue audit reports and certificates. Use of these independent CBs help to address concerns about any potential conflicts of interest. As shown in Figure 1, the cumulative number of excipient GMP certificates has steadily accelerated during the past five years.

Credible third-party certification involves both an independent assessment declaring that specified requirements pertaining to a product, person, process, or management system have been met and also that the certifying body has independent oversight to ensure impartiality and freedom from conflicts of interest. The third-party certification is more robust than first-party certification, in which an individual or organization providing goods or services offers assurance that it meets certain claims, and second-party certification, in which an association to which the individual or organization belongs provides the assurance (1).

Audit options

Unlike the one-day excipient audit conducted by pharmaceutical companies, initial EXCiPACT and NSF-ECP certification programs require several days to complete and include annual surveillance audits. Qualification and verification of auditor competency and independence is key to ensuring the validity of the certification. Using auditors specifically trained and certified to excipient cGMP standards helps ensure consistent and relevant audits. The publication of the certification program, as well as criteria for approving certification bodies and auditors, should be considered as an added value for recognition of certification audits. In addition, in third-party audits, report findings are more likely to be based on excipient GMPs and less prone to auditor bias.

Regulatory acceptance of accredited third-party party audits for assessing the quality and safety of regulated products...
is not new. In October 2002, FDA implemented the Medical Device User Fee and Modernization Act (MDUFA), which authorized third-party Accredited Persons (AP) to conduct medical device facility inspections (8).

Then, based on the agency’s recognition of the increasingly global nature of the industry, and the number of medical device manufacturers, in 2012 the International Medical Device Regulators Forum (IMDRF) designed and adopted the Medical Device Single Audit Program (MDSAP) (9) to allow for greater coverage in auditing manufacturers as opposed to relying solely on government resources from individual countries.

Similarly, based on pioneering work by the Global Food Safety Initiative (GFSI) to develop and implement a voluntary certification program for the food industry, the FDA Food Safety Modernization Act (FSMA) final rule, “Accreditation of Third-Party Certification Bodies to Conduct Food Safety Audits and to Issue Certifications,” established a voluntary program for the accreditation of third-party certification bodies to conduct food safety audits and to issue certifications of foreign facilities and the foods for humans and animals they produce (10).

Relying on these third-party certification programs allows responsible parties to redirect their internal resources toward assessment of any relevant issues that may be outside the scope of the standard.

Although third-party excipient cGMP certification can help pharmaceutical companies verify appropriate excipient cGMPs are in-place and being followed, certification does not exempt a pharmaceutical company from executing and documenting formalized risk assessments to identify appropriate excipient cGMPs based on intended use and criticality. In addition, in some cases a certified excipient cGMP audit report may need to be supplemented with additional information (outside the scope of the standard) to justify use of an excipient. The pharmaceutical company may need to acquire further verification, including but not limited to quality agreements, special questionnaires, teleconference discussions, and even on-site meetings and/or audits to address specific issues or concerns.

**Best practices for utilizing cGMP audit reports**

Through partnering and communication with excipient suppliers, pharmaceutical companies should strive to understand whether a third-party excipient cGMP certification is in place and, if not, whether a supplier might be seeking such certification.

To help justify the acceptance of third-party excipient cGMP audit reports to a regulatory inspector, in lieu of a second-party audit and report, it is important for a pharmaceutical company to develop and document a standard operating procedure (SOP). Establishing SOPs would allow them to promptly utilize the audit report/certificate.

The SOPs should describe the following:

- How the company performs and documents excipient risk assessments to identify appropriate excipient cGMPs based on intended use and criticality
- Details for how the company qualifies the certification program(s) as well as when and how they can use an excipient cGMP certification audit report
- How certificate expiration will be monitored and tracked to ensure its validity
- Where and how audit reports will be received, reviewed, and accepted actions to take if and when an issue arises with excipient quality.

Note: Inappropriate application to products outside the scope of the certification must be avoided. For example, cer-
Third-party audits offer a way to reduce the cost of audits, both for the pharmaceutical manufacturer and the excipient supplier.

**Critical process steps to cGMP certification**

As shown in Figure 2, critical steps in the certification/recertification process include:

- **Step 1—Certification plan.** The excipient supplier develops and documents an internal certification plan including appropriate SOPs for certification, drafting of an audit report, and certificate handling. Best practice is to ensure that the excipient supplier is ready for certification and that any gap assessment is conducted separately from the certifying body audits, to ensure the absence of bias.

- **Step 2—Certification audit.** The excipient supplier schedules a certification audit with a certifying body (communication between supplier and certifying body). The certifying body conducts an excipient GMP audit of the excipient supplier’s facility (this requires communication between supplier and certifying body). Within an agreed upon period of time, the qualified auditor writes a report that is reviewed by a panel of the certifying body, approved, and issued. It is critical that the audit report not contain any confidential or proprietary information about the supplier, because this information could delay providing the report to pharmaceutical companies (this requires communication between the certifying body and the supplier).

- **Step 3—Payment.** The certifying body issues an invoice to the excipient supplier (again, requiring communication between certifying body and supplier). Excipient suppliers pay the invoice, which will not be issued until payment has been received. This step, depends on communication between the supplier and the certifying body.

Note: Payment for an audit by the excipient supplier should not be viewed as a conflict of interest as long as the certification program chosen includes the use of credible, independent, registered, third-party certification bodies employing qualified auditors who are demonstrated to be competent in the relevant standard (11).

- **Step 4—Certificate.** After receipt of payment, the certifying body issues the cGMP certificate to the excipient supplier. After receiving the cGMP certificate, the excipient supplier notifies pharmaceutical customer(s).

- **Step 5—Audit report.** After receiving the audit report from the certifying body, the excipient supplier determines their process for sharing a copy of the report with their pharmaceutical company customer(s).

- **Step 6—Surveillance audit.** The supplier schedules a surveillance audit with the certifying body prior to cGMP certificate expiration, allowing sufficient time for scheduling/executing the audit and invoice payment.

Note: The frequency of certification audits (annually, as required by the EXCiPACT standard) should be compared with the traditional pharmaceutical company audit frequency, which often only occurs every three-to-five years, if at all.

As previously stated, the pharmaceutical company is ultimately responsible for ensuring the quality and safety of the ingredients that it uses for manufacturing. Key questions that pharmaceutical manufacturers should consider when documenting, justifying, and developing a risk ranking and mitigation strategy should include the following:

- Is the certificate from an accredited third-party certification body?
- To what standard was the audit performed?
- What is covered by the standard?
- Has the auditor (training and report) and process been adequately assessed?
- In addition to the cGMP certificate, has a risk assessment been conducted to determine the need for further supplier audits that would cover needs not addressed in a routine audit?
- Have necessary internal SOPs been developed to document the strategy and any necessary steps taken to ensure proper execution?
- Have criticality and ranking of excipients been performed and documented?
- Where are the certificates and audit reports going to be stored?
- Who is responsible for reviewing the audit reports and determining whether the excipient supplier meets defined cGMP requirements?
- Is specific excipient product that is used included within scope of the third-party certification?
- Who is responsible for tracking certificate expiration dates and providing notification for any potential issues?
- Have the necessary agreements/contracts been put in place (e.g., supplier certifications, audit reports, notifications of change, quality agreements, other) with the supplier to ensure a continued supply of excipients that meet the defined GMP requirements?
- Are there items outside the audit/certificate that require follow up with the excipient supplier?
- Is technical due diligence required to achieve the enhanced understanding necessary for pharmaceutical quality by design?
Is there any additional risk involved, or are there concerns that are not stated within the scope of the cGMP audit and certifications?  
Note: Pharmaceutical companies should consider and manage for risks with suppliers and supplied excipients, and should have documented evidence that shows whether or not the supplier is addressing any potential concerns.

When pharmaceutical manufacturers audit suppliers, results can vary depending on the training, experience, and levels of bias among those performing the audits. Third-party audits offer an standards-based alternative.

Follow-up communications required
Often, a third-party audit cannot cover all technical aspects. Therefore, certain proprietary or ad hoc issues or concerns should be addressed via follow-up (phone, email/mail, in-person, other) with the supplier after the audit and audit report. Suppliers who choose to use third-party certification bodies and excipient cGMP audit reports and certificates to support their conformance to excipient cGMPs will need to select certifying bodies that have been qualified and approved by EXCiPACT or NSF-ECP, because these programs will have the ability to:
- Manage for continued certification
- Handle confidential information securely
- Communicate when certification is suspended or withdrawn
- Conduct audits and issue reports within a predefined period of time (e.g., 30 days of audit)
- Provide excipient cGMP certificates without delay together with corresponding audit report
- Provide notification in the event that a certificate is suspended or withdrawn
- Provide notification if scope of certification changes
- Help establish and maintain a channel of communication to facilitate execution of above bulletied items.

Demand for audits is increasing
Today, global regulatory authorities require objective evidence that an excipient supplier has implemented and complies with the principles of cGMP and GDP in the manufacture and distribution of excipients. As a result, an escalating number of second-party audits are being performed, globally, to justify quality and safety compliance of ingredients used in drug products. The sharp increase in the number of these audits is putting a strain on resources at both pharmaceutical companies and excipient suppliers. In addition, the training, experience, and bias from pharmaceutical company auditors is highly variable compared to the standardized qualification requirements of auditor used by third-party certification programs.

Third-party auditing and certification of excipient suppliers can assist in the development, manufacture, and supply of safe and effective medicinal products. Properly executed third-party audit and certification programs referencing consensus-based excipient cGMP and GDP standards, such as EXCiPACT and the NSF/IPEC/ANSI 363 US National Standard, deliver benefits to excipient suppliers and pharmaceutical companies, as well as regulators, by reducing the audit burden without compromising patient safety. Such third-party audit and certification programs raise quality expectations to an industry acceptance level and enhance patient safety.

The concept of third-party cGMP certification offers pharmaceutical manufacturers, excipient suppliers, and regulators a proactive way to ensure cGMP requirements are being met. This approach, already used in the medical devices and food sectors, and offers the pharmaceutical industry an opportunity to improve quality and safety assurance.

References
7. EXCiPACT is a registered trademark of EXCiPACT asbl.
8. FDA Accredited Persons Inspection Program; www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ThirdPartyInspection/ucm125410.htm.
9. FDA Medical Device Single Audit Program (MDSAP); www.fda.gov/MedicalDevices/InternationalPrograms/MDSAPilot/.
11. T. Scott, “Pharmaceutical Excipient Regulations: How the EXCiPACT Certification Scheme can Reduce the Audit Burden for both Suppliers and Users,” Industrial Pharmacy, 57, 4-6 (April 2018).
Patient safety is a top priority at each stage of the manufacturing process and requires an increased attention to detail. There are a number of hurdles to clear when implementing any new initiatives or process changes. Historically, these challenges mean the pharmaceutical industry is slower to innovate and hesitant to adopt new strategies that could improve manufacturing productivity.

Continuous manufacturing has garnered global attention in its ability to alleviate costs, while simultaneously increasing productivity and quality. Thus far, the full potential it offers remains relatively untapped as only two continuous-processed drug products have been submitted and approved. Despite slow adoption, the benefits of continuous manufacturing are clear to manufacturers, and the industry seems optimistic based on drug-product development using continuous manufacturing. As the concept matures and both innovative and generic-drug companies express interest, the question to implement continuous processes will continue to transition from a question of “why” to “how.”

**Understanding the “why”**

Lower pharmaceutical manufacturing costs mean drug products will be more globally accessible and available to patients who need them. Direct-compression tableting is a form of continuous manufacturing that can eliminate expensive and energy-intensive granulation steps to offer a cost-effective solution. In addition, using fewer process steps removes potential sources of variability in the final drug product.

As demonstrated in Table 1, switching to continuous processes that enable direct-compression tableting can help reduce total operating costs by up to 60% and cut time by more than 50% to streamline manufacturing and gain efficiencies (1). Shortened development time and lowered manufacturing costs offer both short- and long-term benefits for drug-product manufacturers as the freed-up resources and time will allow them to focus on other life-saving innovations. The push for a more sustainable planet has also gained continuous manufacturing popularity as companies become increasingly conscious to have a smaller environmental footprint. For the drug-product manufacturer, continuous manufacturing offers the additional benefits of implementing process analytical technology, consequently improving process control...
Flexible, scalable, full-service clinical supply services to take your study from Phase I to Phase IV.

Our innovative solutions leverage our comprehensive services and expertise to create tailored clinical supply solutions that meet your needs, regardless of trial size or complexity. With 8 GMP facilities and 50+ strategically located depots worldwide, we have the local expertise to help speed your molecule to clinic and the global scale to handle virtually any clinical supply need.
Excipients

Continuous manufacturing can significantly save time and energy associated with wet granulation and thus reduce the environmental impact of drug-product manufacturing. Table II reflects the amount of energy and water used in wet-granulation operations. For high-volume drug products (roughly 400 million tablets per year), nearly 50 metric tons of water and 31 megawatt hours of energy per year could be saved through direct compression. Companies that move away from batch-by-batch processing to create more reliable and affordable drug products at a faster rate are at a significant competitive advantage. The need for drug products to be more readily available to patients will only continue to rise. One facet of this demand increase is driven by the rise in aging population. Predictions indicate that in 2050, the number of people aged 80 years or over will reach 434 million globally, having more than tripled in number since 2015 (2). As people are living longer, it will be vital for drug products to be more accessible to ensure quality of life in the aging population.

Understanding the “how”
Companies want to find a way to incorporate new processes without hindering productivity and disrupting processes that have been in place for decades. For many manufacturers, the answer to this challenge is to incorporate excipients in formulations for improved flowability and processability.

Dow Pharma Solutions has responded to the industry-wide trend in switching from batch production to continuous processing with Methocel DC2 hydroxypropyl methylcellulose (HPMC). The technology is engineered to improve dry-powder flow for streamlined matrix-tablet manufacture and improved drug content uniformity. This also helps shorten development time and reduce manufacturing costs by up to 60%.

When choosing excipients, drug-product manufacturers should consider additional attributes of excipients such as particle size, particle morphology, density in relation to impact on powder flowability, compactibility, and the critical quality attributes of excipients impacting performance of the final drug product. To successfully do this, drug manufacturers must partner with suppliers who have rigorously tested their excipients against industry standards and have available data. Drug-product manufacturers who partner with trusted suppliers will have the support needed to ensure they are choosing the strongest fit for their formulation.

By choosing the right technologies and suppliers that have the expertise and experience needed, drug product manufacturers are equipped with the tools necessary to tackle the “how.”

Uptick of excipients in drug formulations
There has been an increased focus on excipients as drug makers continue to explore new ways to take pharmaceutical manufacturing to the next level. Formulations will require new excipients to support evolving continuous-manufacturing processes, and thus

Contin. on page s30
FULL-SERVICE CDMO FOR A GLOBAL MARKET

CordenPharma is your full-service CDMO for a global market. Through our network of technology platforms and cGMP facilities for the manufacture of APIs, Drug Products and pharmaceutical Packing, CordenPharma experts translate your complex processes, ideas and projects at any stage of development into high-value products.

www.cordenpharma.com

TECHNOLOGY PLATFORMS

- PEPTIDES, LIPIDS & CARBOHYDRATES
- HIGHLY POTENT & ONCOLOGY
- INJECTABLES
- SMALL MOLECULES
- ANTIBIOTICS

VISIT US AT
CPhI Worldwide >
Stand 7F30
October 9–11, 2018
Madrid, Spain
Antibody-drug conjugates (ADCs) are targeted therapies that combine a specific antibody or antibody fragment linked to a drug. ADCs have revolutionized the treatment of a number of diseases by enabling more specific drug targeting with fewer side effects. Despite the growing ADC pipeline, Charlie Johnson, CEO of ADC Bio, notes that many promising ADCs are being overlooked because of critical aggregation control problems. Pharmaceutical Technology spoke to Johnson about the limitations of conventional manufacturing techniques used in the production of ADCs and why preventing aggregation at its source is the best solution.

Causes of aggregation

PharmTech: What are the causes of aggregation in ADCs?

Johnson: Aggregation of biomolecules can occur for a variety of reasons. Some antibodies are inherently prone to aggregation, especially when they are maintained in solution under conditions that promote aggregation, for example:

- Unfavorable buffer conditions where either the salt type and/or salt concentration is too low or too high can cause aggregation.
- Aggregation can occur if the system is held at a pH that coincides with the isoelectric point of the antibody (this is the point where the biomolecule carries no net charge and represents the point of least aqueous solubility). This pH may be required, for example, when a particular conjugation chemistry requires a specific pH.
- It is often the case during conjugation that solvents are required to solubilize otherwise poorly soluble payload-linkers, in particular highly hydrophobic ones. Some solvents are known to promote aggregation.

However, the most significant issue that increases the propensity of antibodies to aggregate is the modification of their surfaces through chemical conjugation to hydrophobic payload linkers. Once the payloads are conjugated to the antibody, they present hydrophobic patches that attract hydrophobic areas on other antibodies, thus initiating the aggregation process. Once formed, these low molecular weight aggregates form nuclei sites where further aggregation can occur, eventually leading to high molecular weight aggregates and ultimately precipitation from solution.
Conventional techniques
PharmTech: What are the limitations of conventional manufacturing techniques used in ADC production and why do they fail in preventing aggregation?

Johnson: Conventional conjugation of ADCs occurs in dilute aqueous buffered solutions. The buffer conditions and pH are adjusted to suit the chemical conjugation conditions for attachment of the payload-linker to the antibody. Historically, ADCs have been prepared by conjugation of either naturally occurring lysine or cysteine residues on the antibody, although more recent developments see the use of ‘site-specific’ residues, some of which focus on engineered-in residues (e.g., thiomabs) or through modification of naturally occurring sites on the antibody (e.g., glycan modification). What is common to all conventional conjugations is that eventually the antibody or modified antibody will be exposed to a payload-linker to produce the ADC, and that is commonly the most unstable point in the process for the antibody, because conditions such as buffer composition, concentration, pH, and addition of co-solvents are selected to optimize the conjugation chemistry, not the stability of the antibody.

A degree of aggregation is, therefore, always expected, although the degree to which the antibodies aggregate is mainly determined by the inherent hydrophobicity of the payload itself. Efforts have been made to reduce hydrophobicity of payloads either through modification with solubilizing linkers or modification of the payload structure, but these efforts have not fully solved the problems of aggregation. Aggregation of ADCs is not simply an issue of yield inefficiencies and costs, although these issues can be severe and lead to the unviability of a product.

Aggregates and, in particular, soluble high molecular weight aggregate must be removed as they are immuno- genic and can cause severe allergic reactions if administered. Historically, aggregates are removed from ADCs via application of chromatographic methods such as size exclusion or hydrophobic interaction separation techniques. These approaches add further processing time and cost, and it reduces the yield of the system, which all adds to the cost of producing an ADC.

Preventing aggregation
PharmTech: What’s the solution to such aggregation problems?

Johnson: The best solution to the aggregation problems prevalent with conventional conjugation methodology is to prevent aggregation at its source. If antibodies are held physically separate from each other during the ‘unfavorable’ conditions of conjugation, they cannot aggregate in the first place.

An obvious way to prevent this aggregation is through immobilization of the antibodies on a solid-phase support, such as a resin, and carry out the conjugation of the payload-linker while the antibodies are bound to that support. ADC Bio’s Lock-Release technology uses this approach and can be performed in either batch or flow mode. It is easily scalable in the same way that other chromatography methods are.

The initial step is antibody capture onto the resin, which is analogous to the protein A capture step in downstream processing of antibody manufacture. Once immobilized, the antibodies are sequentially exposed to process reagents and the payload-linker to produce the ADC, with intermediary washing steps to remove excess reagents. At the end of the process, the immobilized ADC is released from the resin into a stabilized buffer matrix that prevents any subsequent aggregation.

Lock-Release processing provides a unique way of preventing aggregation of ADCs at source while ensuring that the ADCs produced are free of contaminants (e.g., free payload-linkers and solvents) that can interfere with in-vitro and in-vivo read-outs and also lead to enhanced toxicity when administered to patients.

ADC manufacturing using Lock-Release is significantly simplified compared to conventional manufacturing, because the process equipment train used is the same irrespective of the ADC being made. Conventional manufacturing, in contrast, will have different requirements in terms of process equipment and hence the manufacturing footprint required depending on the process developed.

Locking mechanism
PharmTech: Can you tell us more about the locking mechanism?

Johnson: Lock-Release at its most basic level is a conceptual way of constructing ADCs on solid supports, designed to improve both the quality of ADCs, the yield, and as a result, the economics of production. ADC Bio has patented multiple methods of Lock-Release. The favored technique to date is based on affinity capture, using mimetic resins. The specific resins used depend on the process in question and, to some extent, where on the antibody the conjugation of the payload-linker is required. As with most affinity capture methods, the release method relies on varying pH and salt concentration. The demonstrated capacity of our Lock-Release resins is in the range 5 to 50 mg per mL of resin, but we expect that this range can be enhanced further.

A significant advantage of using affinity-based capture techniques is that the resin can be re-used over multiple batches, and that the quality of product is extremely high and consistent over multiple batches.

Lock-Release can be run in either stirred batch or column (flow-mode). For manufacturing purposes, flow mode is preferred because it offers predictable linear scale-up with other chromatography-based techniques. As such, the required manufacturing footprint and equipment train remain similar for all Lock-Release-based processes, which offers significant productivity and capital cost advantages over conventional manufacturing techniques at commercial manufacturing scale.
In aseptic and sterile drug fill/finish and inspection, automation can reduce or eliminate operator intervention, which reduces contamination potential and improves efficiency. Traditional, one-axis automation works well for high-speed processes, but multi-axis robotic arms offer repeatability with the flexibility to easily change the process or the type of container being filled. Technology advances have made robotic systems suited for aseptic processing and easy to operate.

While the pharma industry may be more familiar with robotics used in packaging operations, advances in technology, such as “near zero particle generating designs and complete tolerance to in-situ biodecontamination cycles with gaseous hydrogen peroxide” have made robotics compatible with aseptic manufacturing, explains Josh Russell, director of business development and technical sales at AST.

Today’s robotic systems are also easily reprogrammed for changes after the system is set up, without requiring a programming specialist on staff, say suppliers. Some platforms, such as those from AST and Vanrx Pharmasystems, are recipe-driven, and an operator inputs the recipe information—such as the type of container and volume to be dispensed—through a touchscreen interface.

Flexibility for small batches
Flexible and repeatable filling are becoming more crucial due to changes in the biopharma industry, notes Chris Procyshyn, CEO at Vanrx Pharmasystems. “The focus on targeted therapies for smaller patient populations creates a challenge for companies to produce a higher number of smaller batches into different container formats. Biologics, plus new modalities such as cell and gene therapies, are more complex and process intensive. The use of robotics is growing in response to these changes,” explains Procyshyn.

A potential drawback to robotic systems is running speed. “These systems aren’t yet designed to run 500,000 unit batches or produce 100 million units a year. But that’s not where the demand is anyway, and conventional systems weren’t meeting the need for small batch flexibility,” says Procyshyn. “If a company is making high-value drugs into multiple formats or sizes, they want a robust, repeatable process that reduces risk. That happens best with a closed robotic filling system.”

“Traditional aseptic systems are proving to not be well suited to address these personalized therapeutic products be-
cause they lack the ability to efficiently produce low-volume, high-mix batches,” agrees Russell. “However, robotic systems that have recipe-driven operation and the ability to process syringes, vials, and cartridges on a single platform are an ideal solution.” In addition, more companies are finding that robotic systems give them the flexibility, ease of use, and sterility assurance they need to replace manual filling of clinical batches.

“From a staffing standpoint, automating these tedious and repetitive processes reduces the risk associated with precise dosing and employee fatigue, and automation can reduce scrap and rework [compared to manual methods],” adds Walter Langosch, Global Business Development director at ESS Technologies. For example, the company’s TaskMate robotic syringe filler/capper, which was introduced in December 2016, replaces manual methods and can fill and cap up to 15 syringes per minute.

“We clearly see a high demand for robotics in aseptic filling,” says Sebastien Schmitt, Robotics division manager, North America, at Stäubli. One growing use is in automated compounding pharmacies in hospitals, in which robots can be programmed flexibly to produce drugs on demand, adds Schmitt. Robotics provide consistent performance, with less equipment inside an isolator, hence, reducing risk and facilitating maintenance.

Steriline Robotics, a spin-off company created by Steriline with Milan Polytechnic, produces aseptic filling machines primarily used in hospitals and in pharmacy compounding. “The machine we developed uses two robots cooperating to help pharmacies in targeted drug reconstitution for each patient, according to their specific prescription,” notes Federico Fumagalli, chief commercial officer at Steriline.

Steriline is focused on “zero-loss” aseptic filling systems that aim to increase production efficiency and reduce the waste associated with rejects using traditional automation. Their robotic system can, for example, identify a filled vial that is missing a stopper and send it to be stoppered during a second cycle, preventing the loss of that vial, says Fumagalli. Steriline’s systems run faster than some other robotic systems due to their artificial-vision system, reaching a filling speed of almost 100 vials/min, he says.

Solution for nested vials

Nested vials have been available for more than five years, and the technology to optimally handle vials in this format is now catching up, says Russell. In AST’s ASEPTiCell and GENiSYS aseptic filling and closing machines, six-axis articulated robots perform all the critical aseptic operations, including removing the tub from its sterile overbag, opening the tub, and denesting the containers (i.e., vials, syringes, or cartridges). After filling, the robot closes the containers almost immediately, resulting in less time that the sterile drug product is exposed to the aseptic environment.” “The system is completely closed. It eliminates operator intervention and allows a completely aseptic fill,” says Russell. Depending upon the application requirements, the system can be used inside a restricted access barrier system (RABS), isolator, or laminar airflow hood.

The robotic system allows a streamlined deck that is easier to clean than traditional automation, explains Russell. Another advantage over fixed automation is that the robot has various pre-programmed “maintenance positions” where it is ergonomically positioned for operators to access the disposable fluid path and to perform other necessary aseptic tasks without violating basic “first air” principles. In addition, the robotic system enables a real-time fill-weight check. AST’s machine uses an in-process feedback loop to the filling pump for closed-loop control. In addition to the commercial-scale ASEPTiCell i100 line, a laboratory-scale line GENiSYS was introduced in October 2017 for small-scale filling for R&D (e.g., stability studies), for clinical production, and also for small-scale commercial production, such as cell and gene therapy.

Gloveless isolator

A common use of robots in aseptic processing is to use a robot to replace certain operations, such as removing the cover from a nested container tub. Entirely rethinking the aseptic filling process, however, allows manufacturers to take full advantage of robotics. Procysyn explains, “First, robots provide a highly repeatable production process. Using recipe-driven processes, they are able to produce multiple drug products at equally high quality levels into different containers. Second, robotic systems are agile and change quickly between vial, syringe, and cartridge formats. Robots can handle every type of container the same way if the containers and closures are nested, so there are limited change parts. Without traditional electro-mechanical components complicating the machine’s interior, decontamination cycles are much shorter too. Third, robots allow the design of gloveless isolators. A gloveless isolator can run much cleaner than a conventional isolator and be completely closed. [There are] no mouse holes, conveyors, glass-to-glass contact, or sortation bowls, which all create risks to the batch.”

Procysyn notes that Vanrx Pharmasystems SA25 Aseptic Filling Workcell gloveless isolator technology is based on a standard design, which allows filling operations to be built faster than before (with lead times of less than a year) and in less space. The workcell design provides agility, with the ability for one machine to fill multiple container formats with minimal changeover times. “Gloveless isolator technology provides better aseptic assurance than conventional isolators or RABs,” adds Procysyn. The workcells are entirely closed to the outside environment, and they also use single-use product-contact materials.

Contract development and manufacturing organization (CDMO) FUJIFILM Diosynth Biotechnologies announced in a May 23, 2018 press release that it was investing in the SA25 Aseptic Filling Workcell gloveless isolator technology as it expanded its gene therapy and viral vaccine fill/finish capabilities to provide services in support of late-phase candidates and commercial supply (1). Fujifilm highlighted the advantages of automated environmental monitoring and no glass-to-glass contact. Contin. on page s30
The human skin protects the body from physical, mechanical, and chemical insults while preventing endogenous water loss. This function is predominantly achieved by a thin (10–30 μm) cornified outermost layer—the stratum corneum (SC)—generated through terminal differentiation of the basal epidermal keratinocytes. The stratum corneum protects the human body, but also severely limits drug delivery into and across the skin. The historical and theoretical understanding of the type of compound that will permeate the skin is based on the “500-dalton rule” (1, 2), where it is assumed that most compounds permeating the SC have a relatively small molecular weight (<500 Da) and are moderately lipophilic (log P 1–3.5) (3). Such an understanding was, however, based on the assumption of transdermal delivery across healthy skin with an intact barrier. Yet, according to the data from Citeline’s Pipeline database, 7% of topical medicines for the treatment of skin disease contain drugs with molecular weights from 600–1000 Da. Tacrolimus and pimecrolimus (804 Da and 810 Da, respectively), for example, are the two most well-known compounds that appear to contradict the “500-dalton rule.” Nevertheless, at present, there is no approved topical formulation containing a drug with a molecular weight of more than 1000 Da.

**Topical delivery of macromolecules**
The literature consists of publications claiming topical delivery of macromolecules. Why the discrepancy? Critical evaluation of this literature suggests that some of the methodologies can be misleading and may contain artifacts that make translating to a clinical significance difficult. One of the challenges when attempting to understand passive topical delivery of compounds is establishing a model or testing system that mimics the in-vivo condition. This task is even more challenging when the size of the compounds exceeds 1000 Da because many of the analytical tools used to detect and quantify small molecules are problematic for larger molecular weight compounds. Many researchers have used animal models, such as ro-
At present, there is no approved topical formulation containing a drug with a molecular weight of more than 1000 Da.

Tons and/or minipigs, either in vitro or in vivo, to assess the passive delivery of large molecules. It can be argued that these models have yet to show good correlation to the clinical situation as proven by the lack of products on the market. In fact, many of these studies have been shown to be misleading as a result of inappropriate experimental design or a lack of contextualization of this limitation in the study conclusions.

There have been, nonetheless, some glimmers of hope when polysaccharides, proteins, and oligonucleotides are explored. Hyaluronic acid (HA), a naturally occurring polyanionic polysaccharide up to 1000 kDa, is found in the skin and has been shown to be a key molecule involved in skin moisture due to its capacity to retain water (4). There have been many publications investigating the topical delivery of HA. One of the earliest and most comprehensive studies examined the topical delivery of HA following application to the human forearm in situ (5). Tritiated HA was detected in the dermis just below the epidermis, and the authors took many steps to eliminate artifacts to ensure the observations were real and valid. Since publication in 1999, the group did not report further findings on HA. However, there have been many other studies claiming to have shown HA permeation through human skin, yet the topical delivery HA continues to be taken with scepticism (6–11).

In addition, latex proteins have been proposed to cause hypersensitivity allergen-based reactions (12). Latex proteins are larger molecular weight compounds (14–52 kDa); hence, it is interesting how these proteins can produce allergic responses in the skin. It is presumed that the proteins are able to cross the skin barrier to elicit the response. In fact, there are studies that show latex proteins were able to penetrate excised human skin, and that exposure induced an IgG1 response in vivo (13).

There have been several intriguing studies exploring the topical delivery of oligonucleotides within the past decade. Experimental studies using a nuclear factor kappa B decoy oligonucleotide (13 kDa) showed initial promise as a po-
Topical Delivery

One of the challenges when attempting to understand passive topical delivery of compounds is establishing a model or testing system that mimics the *in-vivo* condition.

Topical delivery of aptamers

Aptamers are a subclass of large molecules that have been shown to have high binding affinity and selectivity with the ability to disrupt protein–protein interactions. Currently, it is not possible to disrupt these protein–protein interactions with traditional small molecules. Aptamers, therefore, represent a new class of molecules that could have antibody-like binding affinity with the possibility of topical delivery. Evidence from the literature supports their rapid clearance from the systemic circulation, thus limiting unwanted systemic side effects and restricting the biologic effects of topically administered aptamers to the skin (16). Interestingly, aptamers offer significant conformational plasticity and flexibility. Moreover, their structure can be modified without the loss of significant activity (17, 18).

In a recent publication, researchers at GlaxoSmithKline, University of Reading, and MedPharm showed, for the first time, that a 62-nucleotide (20,395 Da) RNA-based aptamer, highly specific to the human interleukin (IL)-23 cytokine, permeated intact human skin to therapeutically relevant levels in both the epidermis and dermis (19). This observation was particularly surprising considering the compound was 40 times larger than what is commonly accepted as possible for passive topical delivery in the skin.

In the study, the authors used multiple approaches to demonstrate the topical delivery of the aptamers, including fluorescently labeled aptamer, confocal microscopy, and a novel dual hybridization assay that used capture and de-
tection probes with oligonucleotide precipitation to be able to quantify the aptamer at picomolar levels. They showed the IL-23 aptamer delivered into the skin was significantly above the cellular IC$_{50}$ values (119,000-fold > IC$_{50}$ in the epidermis; 3400-fold > IC$_{50}$ in the dermis) when treated topically using a simple cream formulation. This portion of the study used freshly excised human skin and a diffusion cell commonly referred to in-vitro penetration/permeation (IVPT) and is considered the “gold standard” for assessing topical delivery for both biopharmaceutical companies and regulatory agencies. To confirm the IVPT delivery and to help visualize this delivery, confocal microscopy was introduced on sections from the IVPT study, and this aptamer appeared to localize to the intracellular and extracellular compartments within the viable epidermis (see Figure 1). It was interesting that this observation was noted to confirm a previous publication, showing the uptake of a different aptamer into primary human keratinocytes (20). From this independent observation, it could be extrapolated that intracellular and extracellular targets are possible with this technology.

Aptamers are a subclass of large molecules that have been shown to have high binding affinity and selectivity with the ability to disrupt protein–protein interactions.

To ensure the delivery observed with the other techniques was at therapeutic levels and the aptamer was bioavailable, the authors developed a Th17 mediated biological model using ex vivo human skin and showed the IL-23 aptamer was able to suppress IL-17 and IL-22 mRNA production (see Figure 2) following topical application. Interestingly, there may be some structural commonalities between HAs, latex allergens, oligonucleotides, and aptamers, which potentially explain the positive observations for topical delivery; however, this hypothesis requires further investigation. Nevertheless, if this in-vitro work were to be confirmed clinically, this result could present a major breakthrough in dermatology and topical drug delivery as it could open new areas of research and potentially targets that are not accessible using traditional small molecules.

A development strategy for macromolecules

There are several critical experimental parameters required to ensure robust, artifact-free results to allow for improved translation to clinical situations. Some of these experimental parameters are the use of human skin with an intact or uncompromised barrier, clinically relevant dosing volumes, a validated highly sensitive analytical method for extraction and quantitation of the compound, and potentially, confirmation of biological activity and structure using human skin.

The first step is to develop an analytical method to ensure the detection, analysis, and quantitation of the macromolecule is fit for purpose and free from interference. Having duplicate analytical methods using alternate techniques is an ideal approach to further confirm that the observations are valid. As with any topical program, it is imperative that proper preformulation studies occur to establish compound and formulation stability both from a chemical and biological activity sense. The next step is to screen compounds and formulations for passive topical delivery using human skin in vitro. The final and perhaps most crucial step is to ensure the macromolecule is tested for biological activity ideally using ex-vivo skin to assess target engagement from a topical application. Given the counterintuitive challenge of proving topical delivery with macromolecules, study designs tend to include a majority of controls (both negative and positive) to ensure an unbiased, non-artifact, and robust result.

References

Content uniformity, which ensures that API is present in the right quantity in solid dosage forms, both within and between batches, is crucial to maintaining patient safety. Variability in API loading can become a safety problem when patients split tablets, a trend that has become common a way to reduce the cost of prescription drugs (1).

Content uniformity testing requirements, however, may not always be clear, and the process may be taken for granted, which can result in quality problems. Technology is available to automate more of the sample preparation portions of the test, which tend to be the most error-prone. Ishai Nir, small-molecule products manager at Distek, Inc., describes challenges with Pharmaceutical Technology, and discusses a new automated sample preparation system that was recently introduced to the market.

**Content uniformity testing often overlooked**

**PharmTech:** You have often described content uniformity as ‘the overlooked test.’ Given the predominance of generic drugs today, why would such an important quality-control test be overlooked?

**Nir:** Content uniformity, which, technically, is part of the United States Pharmacopoeia (USP) Chapter <905> Uniformity of Dosage Unit (2), is definitely the red-headed stepchild of solid-dosage form testing. For one thing, it is one of the tests where the least detail or guidance is provided on execution.

For example, the entire section of Chapter <905> that covers the procedure for performing the content uniformity (CU) measurement reads, simply: ‘Assay 10 units individually using an appropriate analytical method.’ That’s it! Compare that with Chapter <711>, the dissolution chapter, which uses more than twice the number of words just to describe the specifications of a paddle, one of seven pieces of equipment that are required for dissolution testing. In 2018 alone, Google Scholar currently includes over 5500 references for dissolution testing, yet less than 1300 for content uniformity testing (2).

**PharmTech:** What impact does this lack of definition most often have on results?
ACCELERATE YOUR CONTENT UNIFORMITY

UP TO 90% FASTER SAMPLE PREPARATION

- REPRODUCIBLE, CONSISTENT RESULTS
- 10 INDIVIDUAL STIRRING STATIONS (ALSO AVAILABLE AS A 2 POSITION)
- ADJUSTABLE SPEED & TIME
- VARIETY OF SAMPLE PREPTUBES:
  - 50, 250 and 500 mL
  - CLEAR or AMBER
  - STERILIZED or NON-STERILIZED

AAPS PharmSci 360
Booth #927
Typical sources of error

PharmTech: What types of problems typically show up during CU sample preparation?

Nir: There are two major sources of error in CU sample prep. The first is incomplete API extraction, and the second is dilution errors. Incomplete extraction takes several forms. One major source of variation is due to the fact that, as previously mentioned, unlike dissolution or disintegration testing, these procedures are not performed using a specific apparatus. This task is normally accomplished using non-analytical lab equipment such as magnetic stirrers or sonicators. Because the speed, frequency, or power of these units are not rigorously controlled, these parameters can vary over the lifetime of a unit, and between different units in one lab.

Variation can be even greater between units in different labs. So, if a method calls for sonicating the sample for six hours, that may be equivalent to four hours on one sonicator and eight hours on another. Often, method developers ‘solve’ this problem by calling for an overnight run to avoid these issues.

The second source of errors is the dilution steps. Frequently, the 100% extracted solution is too concentrated to be read directly by analytical instruments and requires one or multiple dilutions. Of course, any time a processing step is added, a greater probability of operator error is introduced.

In the case of sonicating samples, mistakes can be even more likely, because prolonged sonicating will normally heat a solution. If the measurements are taken and dilution performed before the solution has returned to room temperature, it can be easy for a lab technician to make a volumetric measurement mistake due to thermal expansion of the liquid.

PharmTech: Why can’t the entire test be automated? Aren’t solutions already available to do this?

Nir: A few systems have attempted to automate the entire CU process, including both sample prep and analysis. However, they are very expensive, starting at over $100,000 and ranging up to several hundred thousand dollars. In addition, they can be complicated to operate, difficult to validate, and expensive to maintain and keep running. In addition, although they address sample preparation concerns, they also attempt to address analysis, which never was much of a problem to begin with.

The PrepEngine, developed by Distek in conjunction with Two Square Sciences, automates only the sample prep portion of the CU test. The goals behind its development were to make the extraction process considerably faster and more reproducible, and, to the extent possible, to eliminate the need for dilution steps entirely. It was also designed to be considerably less expensive than previous solutions.

PharmTech: How does the equipment work?

Nir: The CU sample prep system uses custom plastic vessels, designed for multiple uses, with a built-in blade and filled with appropriate media to extract the API from the dosage form. The main unit comprises 10 positions (to match the 10 samples required for a CU test), the control electronics, and user interface that allows programming the method parameters.

The several-use (typically five runs) tubes are made of polypropylene, and are designed with internal finning, which helps redirect the dosage form down towards the blade as it is being broken apart and blended into the media. They are available in different volumes to match the concentration required for subsequent analysis without further dilution, whenever possible.
As a result, the operator using the equipment must only make one precise volumetric measurement of room temperature media during the entire measurement process. Finally, the tubes are available in amber for light-sensitive products to avoid sensitization before analysis.

**Variability in API loading can be a problem, especially with generic formulations. Improving content uniformity testing offers a solution.**

**PharmTech**: Why use disposable sample containers?

**Nir**: The situation is similar to that of disposable razors. Regardless of what material one uses to make the blades, they will become duller over time and require more agitation time to guarantee complete extraction.

Extending the sample prep time excessively to ensure complete extraction would not be the best solution. Instead, it is better to limit the number of samples that are ground using a given blade. Some users have taken this concept to the limit, using each tube only once. In this case, the cost of the extra consumables is offset by the elimination of the time and cost associated with cleaning the tubes. This also eliminates the possibility of any product carryover due to inadequate cleaning. Additionally, using each component only once enables pre-sterilization of the tubes for biologics use.

**PharmTech**: How complicated is method development using the CU Sample Prep Station?

**Nir**: Method development using the CU Sample Prep Station is simple because analysis and calculation of the results remains largely the same as existing methods. The only exception is generally eliminating the need to correct for dilutions, which become unnecessary.

The sample prep portion of method development involves optimizing two parameters—agitation speed and duration. This requires conducting CU testing at different speeds and durations and extraction efficiency. The goal is to find the lowest agitation speed that will still guarantee complete release in an acceptable test time.

**PharmTech**: Can you share examples of successful implementations of this technology?

**Nir**: Distek has published results of some internal proof-of-concept work we have done using an over-the-counter pain medicine (in this case, Tylenol Regular Strength 325-mg tablets from Johnson & Johnson) (3). Tylenol tablets were added to sample preparation vessels containing 500 mL of deionized water. The runs were stopped at different time points, and the extracted API concentration was measured using a fiber optic UV system with a probe that was inserted in the tube.

**Figure 1** shows the results of the measurements. For the desired 90-second agitation time, 2500 rpm was clearly a high enough agitation speed to yield complete extraction. **Table I** shows actual Tylenol CU measurement results obtained from 10 tablets using the sample prep station with 90-second agitation at 3000 rpm. The weight corrected results have a mean of 99.5% and %RSD of 0.12%. **USP** Chapter <905> sets the limit of the CU acceptance value (AV) as less than 15.0 for 10 units. For the data set collected, the corresponding AV value computes to be 0.29.

Pharmaceutical manufacturers that have tested the system have reported similar results and reduced overnight testing times to as little as five minutes. One company that has publicly presented its results is Gilead Sciences, Inc., based in Foster City, CA (4), in work involving a spray-dried dispersion tablet. The original method called for three-hour disintegration of the tablet using a magnetic stir bar.

While using this method, Gilead encountered multiple investigations due to incomplete extraction. With the CU sample prep station, however, the company reported being able to reduce extraction time to 30 minutes. More important than the time savings, the failures and corresponding quality investigations stopped. At this point, dozens of units have been installed globally, and regulatory agencies and authorities such as the US Pharmacopeial Convention have also invested in the technology.

**References**

Excipients — contin. from page s16

it is imperative for drug-product manufacturers to have better understanding of excipient properties and variability.

The dependence on excipients has prompted drug manufacturers to work with their suppliers more closely than ever before to ensure their current supply of excipients is consistent and quality is being upheld to control variability. Drug-product manufacturers must partner with trusted suppliers to ensure current excipients are still applicable when transitioning to continuous processing as well as for customization or creation of new excipients to better fit their evolving formulation and manufacturing needs.

The new concept “designed for purpose” has gained popularity amongst drug-product manufacturers and reflects the need for individualized solutions to optimize each manufacturer’s processes. Currently, drug makers are hesitant to use novel excipients. Therefore, industry leaders and regulatory bodies are working together to explore regulatory pathways that would enable the use of novel excipients and ensure new and modified excipients can more readily move through approvals. Knowledgeable suppliers can assist in overcoming this hurdle by developing novel excipients within existing pharmacopeia standards as well as innovating completely new-to-the-world functional polymers. These factors have the potential to impact current regulatory standards and pave the way for a new approval process for novel excipients.

Roadblocks in continuous manufacturing

The pharmaceutical industry transition to continuous manufacturing will be challenging and time-consuming, but the long-term benefits will outweigh the time and money invested.

The first hurdle drug-product manufacturers must clear is the initial startup cost. This cost can include old batch equipment retirement, new technology purchases, new processes implementations that adhere to quality-by-design principles, and staff retraining. To justify the large expenditure, drug-product manufacturers must focus on the long-term benefits of this investment and how continuous manufacturing will eventually be imperative to maintain a competitive edge. Lengthy approval times and inconsistent regulatory requirements across borders create the need for increased collaboration between manufacturer and supplier. The drive for harmonized regulatory standards across country lines and the updating of current approval processes will allow drug-product manufacturers to enjoy a more connected industry landscape. These efforts will revamp industry infrastructure and alleviate some of the challenges associated with adopting continuous technologies.

Lasting legacies of continuous manufacturing

The implementation of continuous manufacturing will bring about many changes that will likely have lasting positive effects on the pharmaceutical industry. Recognizing change at this scale can be time-consuming but manufacturers recognize the positive impact it could have on their business. Many collaborations will be formed between drug-product manufacturers and suppliers to help navigate the complexity of continuous manufacturing. Regulatory agencies are actively engaged in the modernization of drug manufacturing to better facilitate implementation of new technology. The collaboration between industry leaders and regulatory agencies will play a vital role in pharmaceutical advancement.

The nature of continuous manufacturing is an example of the opportunity to thrive with the combination of business- and science-driven approaches. Manufacturers will become increasingly business savvy to maintain a competitive edge. Continuous manufacturing will help satisfy both sides of the spectrum by improving the overall product for formulation ease, patient safety, manufacturing flexibility, while also reducing costs and mitigating risks.

References


Aseptic Filling — contin. from page s21

Vanrx Pharmasystems recently introduced a smaller-scale gloveless isolator system, the Microcell vial filler, designed for rapid scale-out of personalized medicines, such as cell and gene therapies and immuno-oncology products, from clinical through commercial manufacturing. The system replaces manual filling and small-volume filling machines in biosafety cabinets, RABS, or isolators, says the company (2). The Microcell can fill 2R-50R nested vials with toolless changeover and decontamination in 15 minutes.

Cobots

Stäubli’s TX Stericlean series was the first robot introduced in 2008 for aseptic production areas, says the company, which reports that its new TX2 line of collaborative robots (i.e., cobots) are also a first for aseptic processing. The use of cobots allows glove boxes to be located next to the robot, so that the operator can intervene in the isolator without stopping the production process. The TX2 robots are Industry 4.0-compatible, in that they can collect production data and are capable of communicating with each other, reports the company.

References

The editors of Pharmaceutical Technology present this special planning guide for the 2018 CPhI Worldwide trade show, which will be held Oct. 9–11 in Madrid, Spain. This section highlights the exhibition, conference, and networking activities of this leading industry event.

CPhI 2 . . . . . . . . . Highlights
CPhI 4 . . . . . . . . . Introducing bioLIVE
CPhI 6 . . . . . . . . . Exhibition Overview
CPhI 7 . . . . . . . . . Exhibition Floor Plan
CPhI 8 . . . . . . . . . Education Sessions
CPhI 12 . . . . . . . Registration and Travel

Pharmaceutical Technology and CPhI are brands of UBM, a part of Informa PLC.
CPhI Worldwide 2018 Highlights

CPhI Worldwide hosts its 2018 trade show from Oct. 9–11 with a new bioprocessing event—bioLIVE—joining five other pharma industry exhibitions. Conferences, awards, and networking opportunities fill the program.

Comprehensive Exhibition
Tuesday, Oct. 9, 2018: 9:30–17:30
Wednesday, Oct. 10, 2018: 9:30–17:30
Thursday, Oct. 11, 2018: 9:30–16:00
IFEMA, Feria de Madrid, Spain
CPhI Worldwide is home to more than 2500 exhibitors in dedicated zones covering ingredients, APIs, excipients, finished dosage, contract services, packaging, machinery, and more for small-molecule and biologics drugs. Visitors can meet with suppliers of fine chemicals and intermediates, biologic drug development products, drug delivery and devices, supply chain solutions, laboratory equipment and instruments, and contract services. See pages CPhI 6–7 for more information.

Educational Sessions
Tuesday, Oct. 9–Thursday, Oct. 11, 2018
Visitors to CPhI Worldwide can learn about the latest trends, opportunities, and developments in Pharma at free educational sessions located in the exhibit halls.

Pharma Insight Keynotes are a series of educational sessions offering in-depth information on ingredients, outsourcing, packaging, drug pricing, partnerships, and more—presented by bio/pharma industry experts.

During the Pharma Insight Briefings program, company representatives explain the latest trends and technologies for API development, excipients, drug development, manufacturing, packaging, drug delivery, contract services, and more. The Pharma Insight Keynotes and Pharma Insight Briefings are free to attend. See CPhI pages 8–11 for details.

Recognizing Innovation:
CPhI Pharma Awards Gala
Tuesday, Oct. 9, 2018, 18:00–22:30
Eurostars Madrid Tower, Madrid, Spain
The CPhI Pharma Awards honor innovation and excellence in 17 categories. Winners will be announced at the CPhI Pharma Awards Gala on Oct. 9. For additional information, visit awards.cphi.com.

Industry Roundtable Discussions
CPhI Worldwide will host two invitation-only roundtable discussions. The C-Suite Roundtable, held in partnership with SCI, will bring together CEOs and executive leaders from across Pharma to come together to discuss key challenges regarding policy, regulation, industry growth, new markets, and global challenges.

Big Data & Machine Learning for Pharma Summit
In collaboration with Innovation Enterprise
Wednesday Oct. 10, 2018, 9:30–17:30
Room N101, North Convention Centre, IFEMA, Feria de Madrid
Machine learning and the advanced analytics are positioned to solve some pharmaceutical supply chain challenges and inefficiencies that lead to drug shortages, missed sales, and higher prices. At this one-day summit—held in conjunction with the Innovation Enterprise—researchers, data scientists, and engineers will discuss how machine learning and artificial learning can streamline process, increase efficiency, and better understand patients and outcomes. The agenda will include big data and analytics in drug development and discovery, application of machine learning in counterfeit drug detection, pre-clinical discovery, demand planning, and big data in supply chain.


In a second roundtable—in partnership with Clarivate Analytics—representatives from Country Pavilion partners will discuss key challenges regarding import and export strategy, globalization, the regulatory environment, and emerging markets.
Women in Leadership Forum

Empowering Women In Pharma
Sponsored by DuPont

Wednesday, Oct. 10, 2018, 8:00–11:30
Room N106, North Convention Centre,
IFEMA, Feria de Madrid

While company leaders are creating programs to increase diversity in their organizations from board level to entry level, what does this mean for women and how can they work with their peers and colleagues to make this happen?

The fifth annual Women in Leadership Forum focuses on talent acquisition and will open discussions about ways to source and place talent responsibly, ethical recruitment, and working toward bias-free work environments.

This event provides participants with an opportunity to meet peers, hear from senior executives on promoting diversity in the workplace, share wins and losses, and assess strategies for career development.

Agenda
8:00–8:30
Breakfast & Networking

8:30–8:35
Welcome from the Chair
Representative from DuPont

8:35–09:05
Keynote Speaker
Representative from DuPont

9:05–10:10
Sourcing and Retaining Female Talent in Pharma
Panel discussion and Q&A:
• How M&A impacts recruitment, career progression, and talent retention
• Creating and sustaining a pipeline of female talent in Pharma
• Diversity in senior leadership
Moderator: Zarmina Penner, business coach
Panellists:
Representative from DuPont
Denise Johnston, VP global sales, NEMERA
Archana Bhaskar, Chief Human Resources Officer, Dr. Reddy’s Laboratories
Frances Zipp, president and CEO, Lachman Consultants

10:10–11:00: World Café Networking and Group Discussions
Moderator: Helena Demuynck, Authentic Leadership Coach

11:00–11:30: Coffee and Networking

Pre-registration is required. For an updated agenda and speakers visit: cphi.com/europe/women-leadership-forum-cphi-worldwide

CPhI Worldwide 2018 Schedule (As of Aug. 15, 2018)—View www.cphi.com/europe for schedule updates

Tuesday, Oct. 9, 2018

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30–11:00</td>
<td>C-Suite Roundtable (invitation only)</td>
<td>IFEMA, Feria de Madrid, Room S100E</td>
</tr>
<tr>
<td>9:30–17:30</td>
<td>Exhibition Open</td>
<td>IFEMA, Feria de Madrid</td>
</tr>
</tbody>
</table>
| 10:30–17:00| Pharma Insight Keynotes and Pharma Insight Briefings| CPhI Theatre—9C80
ICSE Theatre—1G90
Innopack/P-MEC Theatre—4F121
Pharma Forum, Avenida between Halls 5 and 6 |
| 14:00–17:30| Country Pavilion Roundtable (invitation only)      | North Convention Centre, IFEMA, Feria de Madrid|

Begin at 18:30
CPhI Pharma Awards Gala

Coaches depart IFEMA at 17:30.

Wednesday, Oct. 10, 2018

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30–11:30</td>
<td>Women in Leadership Forum</td>
<td>Room N106, North Convention Centre, IFEMA, Feria de Madrid</td>
</tr>
<tr>
<td>9:30–17:30</td>
<td>Big Data &amp; Machine Learning for Pharma Summit</td>
<td>Room N101, North Convention Centre, IFEMA, Feria de Madrid</td>
</tr>
<tr>
<td>9:30–17:30</td>
<td>Exhibition Open</td>
<td>IFEMA, Feria de Madrid</td>
</tr>
</tbody>
</table>
| 10:30–17:00| Pharma Insight Keynotes and Pharma Insight Briefings| CPhI Theatre—9C80
ICSE Theatre—1G90
Innopack/P-MEC Theatre—4F121
Pharma Forum, Avenida between Halls 5 and 6 |

Thursday, Oct. 11, 2018

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:30–16:00</td>
<td>Exhibition Open</td>
<td>IFEMA, Feria de Madrid</td>
</tr>
</tbody>
</table>
| 10:30–15:40| Pharma Insight Keynotes and Pharma Insight Briefings| CPhI Theatre—9C80
ICSE Theatre—1G90
Innopack/P-MEC Theatre—4F121
Pharma Forum, Avenida between Halls 5 and 6 |
Welcome to bioLIVE

Launched in 2018 and adjacent to CPhI Worldwide, bioLIVE is an exhibition and conference for biopharmaceutical development and manufacturing.

The newest event at CPhI Worldwide, bioLIVE focuses on large-molecule biopharma manufacturing and processing. The exhibition and conference offer exhibits, conferences, commercial presentations, and networking opportunities in a unique environment.

Technologies and services featured at bioLIVE:

- Processing equipment
- Analytical instruments
- Continuous processing systems
- Separation and purification systems
- Quality and analytical services
- Cell line, cell culture, and fermentation
- Cell therapy and gene therapy production
- Automation systems and software
- Formulation services
- Freeze-drying
- Process control, smart lab design, cleanrooms
- Biopharma ingredients
- Contract services and R&D
- Commercialized products, vaccines, and biosimilars.

For updates, see www.bio.live.

bioLIVE exhibiting companies, as of Aug. 15, 2018.

<table>
<thead>
<tr>
<th>Company</th>
<th>Country</th>
<th>Stand</th>
</tr>
</thead>
<tbody>
<tr>
<td>73100</td>
<td>Portugal</td>
<td>12A20</td>
</tr>
<tr>
<td>Abzena</td>
<td>United States</td>
<td>12A26</td>
</tr>
<tr>
<td>Admescope</td>
<td>Finland</td>
<td>12A24</td>
</tr>
<tr>
<td>BIOCOM AG</td>
<td>Germany</td>
<td>12B33</td>
</tr>
<tr>
<td>UAB Biotechpharma</td>
<td>Lithuania</td>
<td>12B31</td>
</tr>
<tr>
<td>BSP Pharmaceuticals S.p.a</td>
<td>Italy</td>
<td>12B14</td>
</tr>
<tr>
<td>c-LEcta GmbH</td>
<td>Germany</td>
<td>12A30</td>
</tr>
<tr>
<td>China Chamber of Commerce of Medicines &amp; Health Products</td>
<td>China</td>
<td>12D30</td>
</tr>
<tr>
<td>Dow Chemical Company</td>
<td>Switzerland</td>
<td>12C31</td>
</tr>
<tr>
<td>Frontier Biotechnologies Inc.</td>
<td>China</td>
<td>12B11</td>
</tr>
<tr>
<td>GeneScience Pharmaceuticals Co., Ltd.</td>
<td>China</td>
<td>12A33</td>
</tr>
<tr>
<td>HORIBA</td>
<td>United Kingdom</td>
<td>12B30</td>
</tr>
<tr>
<td>Jilin Qijian Bio-pharmaceutical Co. Ltd</td>
<td>China</td>
<td>12A32</td>
</tr>
<tr>
<td>Luina Bio Pty Ltd</td>
<td>Australia</td>
<td>12C30</td>
</tr>
<tr>
<td>M J Biotech Private Limited</td>
<td>India</td>
<td>12B10</td>
</tr>
<tr>
<td>MabPlex International</td>
<td>United States</td>
<td>12C12</td>
</tr>
<tr>
<td>Nanogen Pharmaceutical Biotechnology JSC</td>
<td>Vietnam</td>
<td>12D20</td>
</tr>
<tr>
<td>Prestige BioPharma Pte. Ltd.</td>
<td>Singapore</td>
<td>12A22</td>
</tr>
<tr>
<td>Quantumzyme LLP</td>
<td>India</td>
<td>12C22</td>
</tr>
<tr>
<td>Rousselot Netherlands</td>
<td>Netherlands</td>
<td>12B13</td>
</tr>
<tr>
<td>Samsung Biologics</td>
<td>South Korea</td>
<td>12C14</td>
</tr>
<tr>
<td>Sekisui</td>
<td>United Kingdom</td>
<td>12C10</td>
</tr>
<tr>
<td>SINOVAC BIOTECH CO., LTD.</td>
<td>China</td>
<td>12D24</td>
</tr>
</tbody>
</table>
bioLIVE Conference Programming
bioLIVE offers free, comprehensive content programs addressing key trends in bioprocessing and manufacturing. High-level commercial and technical content sessions are open to registered visitors and are free to attend.

The Content Dome will host keynotes, panel discussions, and fireside chats on key topics in the following focus areas.

Accelerating Bioprocessing Innovation: The Intersection of Business and Science
Bioprocessing business and scientific leaders discuss the future of the bioprocessing market, highlighting current thinking around how different industry innovations will transform the bioprocessing market for the year 2024 and beyond.

Cell Therapies and Gene Therapies
Cell therapies and gene therapies present an exciting and innovative area of biopharmaceutical development; however, sophisticated manufacturing technologies and processes are needed to bring these new products to market. This module will focus on the latest strategies for overcoming these manufacturing challenges.

Artificial Intelligence and the Future of Biomanufacturing: Identifying Fact from Fiction
The interest in artificial intelligence (AI)-driven solutions for early-stage drug discovery is growing steadily with a projected market volume reaching US$10 billion by 2024 for AI-based medical imaging, diagnostics, personal AI assistants, drug discovery, and genomics. Industry visionaries will review the latest developments in AI as well as practical case study applications in the biopharma space.

Building a Skilled Bioprocessing Workforce Discussion and Real-World Training Sessions
Rapid growth of the biopharma sector, combined with the shortage of skilled workers, mean effective hiring and retention strategies are essential for any biopharma company to ensure continued growth. This session, led by National Institute for Bioprocessing Research and Training (NIBRT), will address the biggest challenge the industry is facing—a lack of a skilled workforce.

Additional features at bioLIVE
bioLIVE Insights Theatre
Hear about the latest products, solutions, and innovations from bioLIVE exhibitors.

Start-Up Hub
Learn about the latest innovations emerging from start-up companies that are developing the solutions of tomorrow.

Introduction to Bioprocessing Breakfast Meeting
In partnership with the National Institute for Bioprocessing Research and Training (NIBRT)
Wednesday, Oct. 10, 2018, 8:30–10:00
bioLIVE Insights Theatre, Hall 12
Small-molecule drug companies looking to enter biologics can gather insights on how to break into the biologics sector.

Lunch Briefing: The Importance of Gelatin and its Endotoxin Level for Applications in Regenerative Medicine
Sponsored by Rousselot
Wednesday, Oct. 10, 2018, 12:30–14:00,
bioLIVE Content Dome, Hall 12
In this free-to-attend session, delegates will learn about gelatin and its endotoxin level for applications in regenerative medicine.

Visit bio.live/content-programme for updates.

Registration
A Visitor’s pass to bioLIVE provides access to all CPhI events. See page CPhI 12 for details.

bioLIVE Speaker Highlights
Confirmed speakers, as of Aug. 22 2018, include:
- John Liddell, senior scientific advisor, The Center for Process Innovation
- Maria Agustina Duguine, owner, Global Regulatory Affairs and Consulting and professor BA Chemistry, UB University Argentina
- Dawn Ecker, consultant and bioTRAK database manager, BioProcess Technology Consultants
- Alan Moore, vice-president and commercial chief for advanced therapies, WuXi Advanced Therapies
- Killian O’Driscoll, director of projects, NIBRT
- John Milne, training director, NIBRT
- Ronald Kompier, managing director, Biotech Training Facility
- Ronald Kander, dean, Kanbar College and associate provost for applied research, Jefferson University
- Amy Peck, founder and CEO, EndeavorVR
- Samet Yildirim, technology innovation manager, Boehringer Ingelheim
- Philip Ridley Smith, sales/marketing director, Cobra Biologics
- Paul Thorning, CEO, Crystec Pharma
- Behnam A. Baghbaderani, global head of process development, emerging technologies, Lonza
- Ryan Wilson, head of Live-Bio therapeutics programmes, Quay Pharmaceuticals
- Peter Shapiro, editor in chief, PharmSource
CPhI Expands to Six Events

CPhI and its co-located events cover the small-molecule and biologic-drug markets with the addition of bioLIVE, an adjacent event for biopharmaceutical development and manufacturing.

More than 45,000 bio/pharmaceutical professionals from 150 countries will converge on Madrid, Spain to explore five co-located events—CPhI, ICSE, P-MEC, FDF, and InnoPack—and a new adjacent event, bioLIVE, at CPhI Worldwide from Oct. 9–11, 2018.

More than 2500 vendors will showcase APIs, excipients, equipment, packaging, contract services, and more for the development and manufacture of small- and large-molecule drugs.

Launching in 2018, the bioLIVE event will focus on advances in biologic drug development and manufacturing through exhibits, educational sessions, and networking opportunities.

The facility floorplan on page CPhI x provides an overview of IFEMA, Feria de Madrid, site of the event. For detailed floor plans of each exhibit hall and location of exhibitors, see https://ubm.cphi.com/europe/exhibit/floor_plan/

Visitors can attend all co-located events—CPhI, ICSE, bioLIVE, P-MEC, FDF, and InnoPack—with one exhibition pass.

CPhI Worldwide
CPhI Worldwide exhibits are arranged in product category zones:
- APIs: Halls 3, 5, 6, 7, 8, 10
- Custom Manufacturing: Hall 10
- Excipients: Hall 8
- Fine Chemicals and Intermediates: Hall 10
- Integrated Pharma: Halls 7, 9
- Natural Extracts: Hall 5

ICSE: Contract Services
Outsourcing solution providers that offer clinical trials, contract research, contract manufacturing, biotech, IT, analytical services, packaging, and logistics services are showcased in the ICSE exhibition in Exhibit Halls 1 and 3.

InnoPack: Pharmaceutical Packaging and Drug Delivery Systems
InnoPack, located in Halls 2 and 4, features a labeling zone, products and services for primary, secondary, and tertiary packaging industries, as well as drug-delivery system suppliers.

P-MEC
Located in Hall 4, P-MEC features machinery and equipment for pharmaceutical drugs.

CPhI Exhibition Hours
- Tuesday, Oct. 9, 2018: 9:30–17:30
- Wednesday, Oct. 10, 2018: 9:30–17:30
- Thursday, Oct. 11, 2018: 9:30–16:00

Finished Dosage Formulation (FDF)
FDF in Halls 12, 14.0, and 14.1 targets the formulation supply chain including pharma, contract manufacturing, out-licensing specialists, end-product distributors, and generic-drug companies. Solid dose, semi-solid, liquids, sprays, and sterile forms including tablets, capsules, gels, parenteral drugs, vials, patches, creams, inhalation, nasal, sublingual, and suppository forms are represented.

bioLIVE
A new event for 2018, bioLIVE will run adjacent to CPhI Worldwide and be located in Hall 12. bioLIVE is dedicated to drug development and manufacturing processes for biologic-based drugs. See pages CPhI 4–5 for details.

Special Activities

Live Pharma Connect
Visitors and exhibitors at CPhI and co-located events can use the Live Pharma Connect online portal to arrange onsite meetings. Using an automated matching system, the service eliminates the need to manually search databases to find business connections. Face-to-face meetings can take place in the dedicated Live Pharma Connect Match & Meet area or at the exhibitor’s stand. Learn more online at www.cphi.com/europe/live-pharma-connect-match-meet-service.

Innovation Gallery
The Innovation Gallery is a showcase for new products introduced at CPhI Worldwide. Visitors can view innovation in pharmaceutical ingredients, finished dosage formulation, contract services, and packaging in three galleries spanning CPhI/FDF, ICSE, and InnoPack. Admission is free to all visitors.
CPhI Worldwide visitors can stay current on technologies, ingredients, manufacturing and packaging practices, and business strategies by attending Pharma Insight Briefings.

At CPhI Worldwide, visitors can learn from experts who share insights, opinions, and technical updates in Pharma Insight Briefings. The 30-minute sessions are held in open-plan theatres on the show floor. The keynote sessions offer in-depth information by industry experts. Briefings cover the latest technologies, services, and product offerings.

All sessions are free to attend. Session and speaker information is as of Aug. 22, 2018. For updates visit cphi.com/europe/agenda.

**CPhI: APIs, Excipients, and Drug Delivery**
Location: CPhI Theatre—9C80

**KEYNOTE SESSION**
Tuesday, Oct. 9, 2018, 10:30–11:00
Analyzing Complex Data in the Pharmaceutical Industry: The Case for Multivariate Analysis
Mike Tobyn, research fellow, Bristol-Myers Squibb

**KEYNOTE SESSION**
Tuesday, Oct. 9, 2018, 11:10–11:40
Quality by Design
Amina Faham, executive board member, International Pharmaceutical Excipients Council Europe

**PHARMA INSIGHT BRIEFINGS**
Tuesday, Oct. 9, 2018, 11:50–12:20
Innovative Gelatine Product to Manufacture Enteric Soft Capsules in One Step
Martin Junginger, product manager pharma gelatine, Gelita

Tuesday, Oct. 9, 2018, 12:30–13:00
A Novel Method for Delivering Hygroscopic Pharmaceutical Drugs
Susana Ecenarro Probst, director of scientific business development, Qualicaps

Tuesday, Oct. 9, 2018, 13:10–13:40
Biological Assays: Responding to Increasing Demands in the Release of Peptide-Based APIs
Michael Postlethwaite, business development manager, Bachem

**KEYNOTE SESSION**
Wednesday, Oct. 10, 2018, 11:10–11:40
Brexit: The Wider Implications for the Pharmaceutical Sector in Partnership with SCI

**PHARMA INSIGHT BRIEFINGS**
Wednesday, Oct. 10, 2018, 11:50–12:20
Champagne Taste for Beer Price? Metabolomic and Isotopic Fingerprint of Commercial Saw Palmetto Extracts
Roberto Pace, vice corporate quality director, Indena

Wednesday, Oct. 10, 2018, 13:10–13:40
Best Practices for Highly Potent API (HPAPI) Development and Manufacturing
Maurits Janssen, senior director, head of commercial development for API, Lonza
**Pharma Forum Theatre**

**Pharma Forum, Avenida between Halls 5 and 6**

**Tuesday, Oct. 9, 2018, 10:30–11:40**

**Panel Discussion: Pricing and Affordability:** Creating a Sustainable Market  
Moderator: Maarten van Baelen, market access director, Medicines for Europe  
Victor Lino Mendonça, head of policy and market access – Europe, Mylan GmbH  
Melek Bostanci Önel, head of regulatory affairs, quality assurance and quality compliance, Boehringer Ingelheim

**Wednesday, Oct. 10, 2018, 10:30–11:00**

**Impact of Generics, Biosimilars, and Next-In-Class Biologics on Access to the State-of-the-Art Treatment of Oncology and Autoimmune Diseases**  
Roman Ivanov, Vice-President, R&D, BIOCAD

**Wednesday, Oct. 10, 2018, 11:10–11:40**

**Russia: Market Outlook & Access**  
Victor Dmitriev, director, Association of Russian Pharmaceutical Manufacturers

**Wednesday, Oct. 10, 2018, 13:10–13:40**

**Production of Chemical Specialties in the Czech Republic**  
Ivan Soucek, director of the association Association of Chemical Industry of the Czech Republic

**Thursday, Oct. 11, 2018, 10:30–11:00**

**Generics in China**  
Amit Bansal, head–global generics, Sanofi India

**Thursday, Oct. 11, 2018, 11:10–11:40**

**What’s the New Scenario for Biological Products and Biosimilars?**  
Uwe Guđat, head of clinical safety and pharmacovigilance, Fresenius Kabi SwissBioSim GmbH

**Wednesday, Oct. 10, 2018, 13:50–14:20**

**Improve Your Bioprocesses with Innovative Salt:** Novel Scientific Data on Iron Salts  
Henning Kuhz, project manager biopharma, Dr. Paul Lohmann GmbH KG

**Wednesday, Oct. 10, 2018, 15:50–16:20**

**Krill Oil Supplementation for Improving Skin Hydration and Elasticity in Adults**  
Andreas Berg Storsve, director R&D, Aker Biomarine

**KEYNOTE SESSION**

Thursday, Oct. 11, 2018, 10:30–11:00  
**The Future is Digital and What This Means for Pharma**  
Aurelio Arias, senior consultant, IQVIA

**KEYNOTE SESSION**

Thursday, Oct. 11, 2018, 11:10–11:40  
**Logistics: A Point of View from Outside Pharma**  
Fernanda Teles, QA RCR director for MLEMEA, DHL Supply Chain

**ICSE: Outsourcing Formulation and Manufacturing**  
Location: ICSE Theatre—1G90

**KEYNOTE SESSION**

Tuesday, Oct. 9, 2018, 10:30–11:00  
**Fireside Chat: CDMO Outlook: “What Ifs” in the 5-year Plan**  
Jim Miller, former president of PharmSource

**KEYNOTE SESSION Powered by bioLIVE**

Tuesday, Oct. 9, 2018, 11:10–11:40  
**Are There Learnings between Bioprocessing and Small-Molecule Production?**  
Lukas Utiger, division president, drug product and pharma development service, North America, Patheon – part of Thermo Fisher Scientific

**PHARMA INSIGHT BRIEFINGS**

Tuesday, Oct. 9, 2018, 10:30–11:40  
**The Vast Opportunities in the Emerging Markets for OTC and Pharma Players**  
Reiner Christensen, CEO, Chameleon Pharma

Tuesday, Oct. 9, 2018, 11:10–12:20  
**Generics in China**  
Amit Bansal, head–global generics, Sanofi India

Tuesday, Oct. 9, 2018, 12:30–13:00  
**The Journey of Revealing Unknowns and Impurities by Material Knowledge**  
Lise Vanderkelen, department head of microbiology and pharmaceutical services, Nelson Labs

Tuesday, Oct. 9, 2018, 13:10–13:40  
**Is Your Product Sterile or Sterilized? Comparison between Aseptic Processing and Terminal Sterilization**  
Annick Gillet, quality manager, Sterigenics

Tuesday, Oct. 9, 2018, 14:30–15:00  
**What’s Next for Sterile Contract Manufacturing in Emerging Markets?**  
Laura Pandolfi, business development manager product partnering sterile pharmaceuticals, Europe, LAM, frica and Asia, Fresenius Kabi

Tuesday, Oct. 9, 2018, 15:10–15:40  
**Technology Selection Methodologies for Addressing Bioavailability Challenges**  
Caroline Bauer, pharmaceutical development manager, Lonza Ploermel
Tuesday, Oct. 9, 2018, 15:50–16:20
Recipharm Pathway to Clinic—From Formulation to Clinical Trial
Mikael Bisra, development and technology sales director, Recipharm

KEYNOTE SESSION
Wednesday, Oct. 10, 2018, 10:30–11:40
Panel Discussion: M&A Outlook for Pharma
Moderator: Kevin Bottomley, partner, Results International
Gérard Bellettre, director, strategic planning, investments and business development – industrial affairs, Sanofi
Tim Tyson, chairman & CEO, Avara Pharmaceutical Services
Mark Quick, EVP corporate development, Recipharm AB
Tim Kent, VP business development global supply, Pfizer

PHARMA INSIGHT BRIEFINGS
Wednesday, Oct. 10, 2018, 11:50–12:20
Compaction Simulation as a Powerful Quality-by-Design Tool: How We Optimize Prototyping, Scale-up, and Even Production Equipment Workload of Complex Oral Solid Dosage Forms
Aline Moulin, senior project manager—pharmaceutical development, Skyepharma

Wednesday, Oct. 10, 2018, 13:50–14:20
ALCOA Data Integrity Assessment
Francesco Amarosi, vice-president business development, PQE

Wednesday, Oct. 10, 2018, 15:10–15:40
Specialty Containers: PVC-free Freeflex Bags and Pre-filled Syringes for Sterile Drug Products
Gabriele Pfaffenthaler, key accounts and business development manager product partnering sterile pharmaceuticals Central Europe, Fresenius KABI

Wednesday, Oct. 10, 2018, 15:50–16:20
Managing the Pharmaceutical Supply Chain
Lynne Byers, executive director, pharma biotech, NSF International

Wednesday, Oct. 10, 2018, 16:30–17:00
Accessing the European Market
Alberto Carazo Fornieles, pharmaceutical scientific advisory director, Azierta

KEYNOTE SESSION
Thursday, Oct. 11, 2018, 10:30–11:40
Discussion Panel: Creating an Industry 4.0 Strategy as Part of Your Manufacturing Plan to Improve Agility, Minimize Time, and Optimize Manufacturing Quality
Michalis Avgoulis, plant automation lead, Johnson & Johnson

PHARMA INSIGHT BRIEFINGS
Thursday, Oct. 11, 2018, 12:30–13:00
CIS Market: Regulatory Strategies in Dynamic Convergence
Polina Dombure, member of the board, Inpharmatis, SIA

Thursday, Oct. 11, 2018, 13:50–14:20
Third-Party Voluntary Evaluation of APIs and Intermediates
Codema Pharma

Innopath/P-MEC: Packaging and Manufacturing
Innopath/P-MEC Theatre—4F121

KEYNOTE SESSION
Tuesday, Oct. 9, 2018, 10:30–11:00
Latest Consumer Trends in Packaging: Pharma Perspective
Chakravarthi AVPS, Global Ambassador, World Packaging Organisation
KEYNOTE SESSION
Tuesday, Oct. 9, 2018, 11:10–11:40
A Personal Approach to Pharma Packaging: Shifting from Large Volumes to Personalized Solutions
Christopher Waterhouse, managing director, IDIPAC

PHARMA INSIGHT BRIEFINGS
Tuesday, Oct. 9, 2018, 11:50–12:20
Debunking the Leachable Myths of Gamma Sterilization: A Migration Study of Steam vs. Gamma
Julie Suman, president, Next Breath

Tuesday, Oct. 9, 2018, 12:30–13:00
Portable Care for Your Respiratory Tract: Exploring New Technology Platforms
Guenter Nadler, director business development, Aptar Pharma

Tuesday, Oct. 9, 2018, 13:10–13:40
Primary Packaging Solutions for Wearable Injectors
Dominique Bauert, head of business development, SCHOTT Pharmaceutical Systems

Tuesday, Oct. 9, 2018, 13:50–14:20
The Best Plastic Vial and Syringe for Biologics
Kenichiro Usuda, researcher, Mitsubishi Gas and Chemical Inc.

Tuesday, Oct. 9, 2018, 14:30–15:00
An Optimized Packaging Solution Designed Around Biologic Drug Products Key Attributes
Martina Largoni, OMPI Pharmaceutical Systems EZ-Fill, OMPI

Tuesday, Oct. 9, 2018, 15:50–16:20
Fake Drugs Pose a Serious Threat to Consumers
Alastair Taylor, vice-president of sales, Systech Europe

Tuesday, Oct. 9, 2018, 16:30–17:00
High-Performance, Solvent-free, Heat-Seal Coating for Pharmaceutical Blister Packaging
Sanjeev Kulkarni, vice-president, R&D and new technology, Bilcare Mitsui Chemicals Inc.
Hiroaki Sugasawa, director, overseas business development, Mitsui Chemicals Inc.

KEYNOTE SESSION
Wednesday, Oct. 10, 2018, 10:30–11:40
Pharmaceutical Packaging Innovations: Collaboration from Fundamental Science to Industrialization
Clive Badman, OBE, executive director, Business Engagement Group, University of Strathclyde
Jagjit Singh Srai, head of Centre for International Manufacturing, Institute for Manufacturing, Department of Engineering, University of Cambridge

PHARMA INSIGHT BRIEFINGS
Wednesday, Oct. 10, 2018, 11:50–12:20
Antimicrobial Protection by the Matter’s Power: Application to Pharmaceutical Products to Replace Preservatives and Better Protect Patients
Loic Marchin, CEO, SAS Pylote

Wednesday, Oct. 10, 2018, 12:30–13:00
Evolution of Raman into Preferred Method for Pharma QA/QC Analysis
Enrique Lozano Diz, business development, B&W Tek

Wednesday, Oct. 10, 2018, 13:10–13:40
Modern Approaches to Pharma QC
Lester Taylor, pharma marketing manager, Agilent

Wednesday, Oct. 10, 2018, 13:50–14:20
Building a Connected Devices Eco-System for Digital Medicines
Sai Shankar, business development director for connected devices, Aptar

Wednesday, Oct. 10, 2018, 14:30–15:00
Container Closure Integrity Testing of Sterile Pharmaceutical Products
Derek Duncan, Director Product Line, Light House Instruments

Wednesday, Oct. 10, 2018, 15:10–15:40
Moulding the Future? How Moulded Glass is Supporting Biotechs and OTC
Moderator: Jean-Paul Judson, public affairs manager, FEVE
Frédéric Jailloux, managing director, VAL-U Advisory
Laurent Zuber, chief commercial officer, SGD Pharma

Wednesday, Oct. 10, 2018, 15:50–16:20
Tracking on Primary Packaging with Anti-Counterfeiting Feature
Jan Luccarda, CSO pharma and medical, Stoelzle-Oberglas GmbH

Wednesday, Oct. 10, 2018, 16:30–17:00
Exploring the Advantages of Prefillable COP Polymer Syringes
Bernd Zeiss, manager technical support medical systems, Gerresheimer

KEYNOTE SESSION
Thursday, Oct. 11, 2018, 10:30–11:00
Workshop: The Future of Sustainability in Pharmaceutical Packaging
Victor Bell, president, EPI - Global Environmental Packaging & Product Stewardship Consultants
2018 CPhI Registration and Travel

Madrid, Spain is host to the 2018 CPhI Worldwide event. The following location, transportation, registration, and travel information can assist visitors in planning their time at CPhI.

Exhibition Hours
Oct. 9, 2018: 9:30–17:30
Oct. 10, 2018: 9:30–17:30
Oct. 11, 2018: 9:30–16:00

Location
IFEMA-Feria de Madrid is located at Avda. del Partenón, 5, 28042 Madrid, Spain, a 10-minute ride from the Barajas International Airport and 15 kilometers from the city center. The facility is accessible by taxi, automobile, Metro, and bus. Visit www.ifema.es for details.

By taxi
Accessible at each entrance to the exhibition complex, more than 15,000 taxis are available to visitors to Feria de Madrid.

By car
Feria de Madrid is linked by road to Madrid’s major access routes and ring roads: the M11 (Exits 5 and 7), the M40 (Exits 5, 6, and 7) and the A2 (Exit 7). The South, North, and East Entrances to the exhibition complex provide direct access to parking areas.

By Metro
Feria de Madrid can be accessed via the Feria de Madrid station on Line 8, whose exit is at the South Entrance of the complex. Line 8 also connects the exhibition complexes terminals of Barajas International Airport.

By bus
A bus network provides access to Feria de Madrid from different points in the city:
• Route 112-Feria de Madrid-Bº Aeropuerto.
• Route 122-Avda. de América-Feria de Madrid.
• Route 828-Universidad Autónoma-Alcobendas-Canillejas-Feria de Madrid.

Registration
Registration provides access to CPhI and co-located exhibitions ICSE, P-MEC, FDF, InnoPack, and bioLIVE, as well as prearranged meetings with exhibitors at exhibitors’ stands or the Live Pharma Connect Stand. Visitor registration is free of charge when registered online until Sept. 9, 2018.
A fee of €50 is charged from Sept. 10–23, 2018.
A fee €140 is applicable on or after Sept. 24, 2018.

The upgraded VIP package includes access to VIP lounges, fast track entry, and access to Happy Hours.
The Exclusive VIP package includes the basic and VIP offerings, plus reserved seating for Pharma Insight Briefings and Women in Leadership Forum, a dedicated cloakroom, a video interview, and entrance to the CPhI Pharma Awards Gala. Visit www.cphi.com/europe/visit/packages-and-prices for details.
No one under 18 years of age will be admitted.

Travel Arrangements
Hotels
b network, the official accommodation agency for CPhI in 2018, has secured accommodations at different price points and can assist with accommodation bookings at more than 100 properties in Madrid.

Air Travel
SkyTeam is the Official Alliance Network for air travel to CPhI, offers travel savings up to 15% and no fees for online bookings.

Visas
CPhI can provide Visa application assistance to all visitors who require it. See www.cphi.com/europe/registration-visa for travel information and details.

Ad Index

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catalent Pharma Solutions</td>
<td>s15</td>
</tr>
<tr>
<td>Corden Pharma International</td>
<td>s17</td>
</tr>
<tr>
<td>Distek Inc</td>
<td>s27</td>
</tr>
<tr>
<td>Grifols International SA</td>
<td>s9</td>
</tr>
<tr>
<td>Lonza</td>
<td>Cover 2, Cover 4</td>
</tr>
<tr>
<td>Steris</td>
<td>s7</td>
</tr>
<tr>
<td>Veltek Associates</td>
<td>Cover 3</td>
</tr>
</tbody>
</table>
SMA MicroParticle ICS
Non-Viable Particle Counters

THE NEXT LEVEL OF PARTICLE COUNTING

UNMATCHED ENVIRONMENTAL CONTROL

STERILE.COM
For more information, visit our website at sterile.com/particlecounters
the next highly potent compound...

Let’s develop it together.

Specialty expertise in highly potent APIs

Identifying a collaboration partner that can meet the aggressive timelines often associated with highly potent drug candidates is critical. At Lonza Pharma & Biotech, we offer the necessary development, upscaling and manufacturing capabilities under full containment that support API handling to exposure levels to 1ng/m³.

We also offer particle engineering (particle size reduction and spray drying) under isolation as well as specialized dosage forms designed for highly potent, low dose applications. We have more than 20 years’ track record in HPAPI manufacturing and compressed scale-up timelines.

A partner that you can count on for all aspects of your drug program – Lonza.