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APIs, Excipients, & Manufacturing 2018

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

API-in-capsule approaches enable pharmaceutical companies to quickly assess new drug candidates with reduced API consumption and to increase speed to clinic.

Jeff Williamson
is director of Product Development at Lonza.

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 programme, 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.

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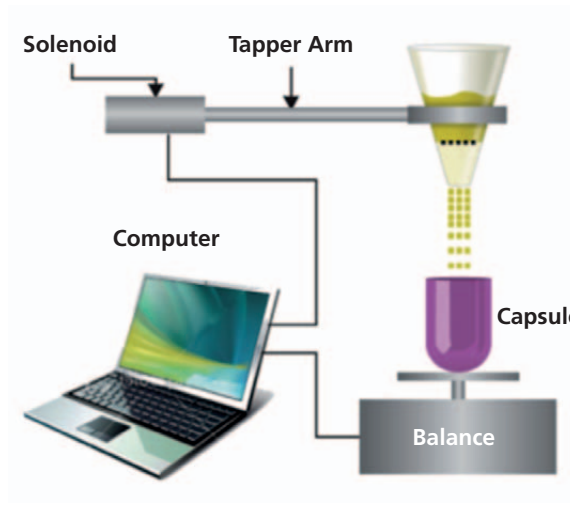
Figure 1: Xcelodose design principle.



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 programme 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 programme. More importantly, if the programme 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

Figures are courtesy of the author.

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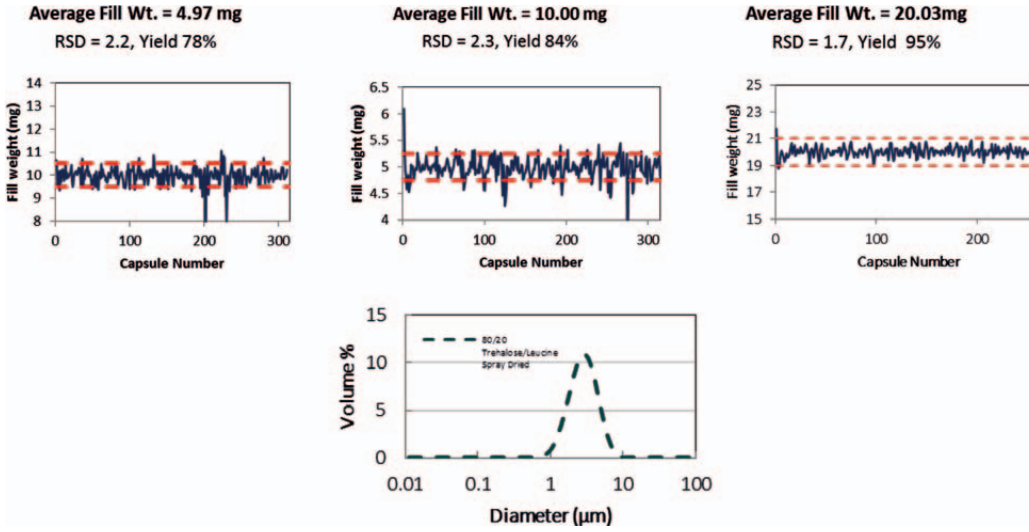
Figure 2: Multiple dosing fill weight ranges using micro-dosing in dry powder inhaler (DPI) formulations.



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.

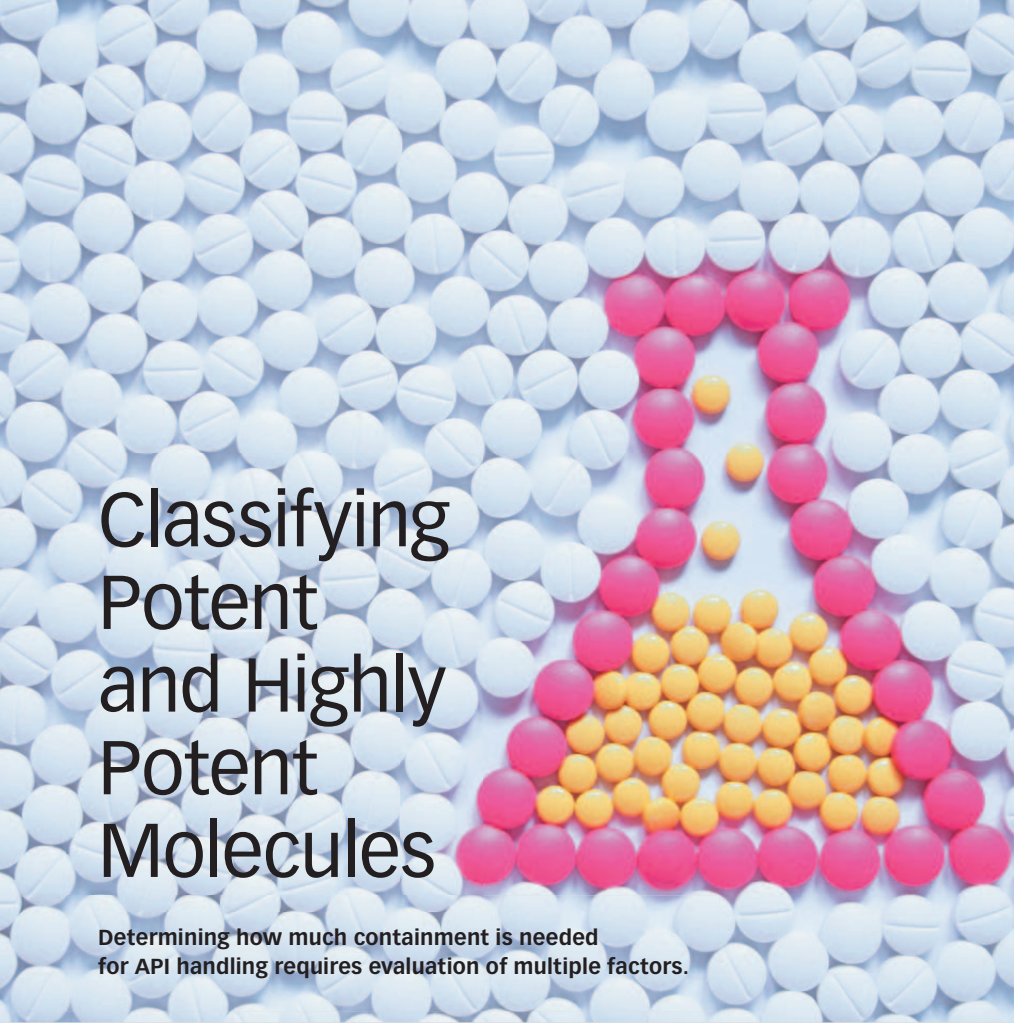
Case studies of micro-dosing applications

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 programme 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 programme 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 paediatric 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 reformulation 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 paediatric 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.

Contin. on page s15



Classifying Potent and Highly Potent Molecules

Determining how much containment is needed for API handling requires evaluation of multiple factors.

Jeff Pavlovich is senior process safety engineer at Cambrex.

Highly potent drugs represent a growing proportion of medicines, including therapies in development and those commercially available. As older products reach patent expiry, generic-drug companies are also moving into this space, creating an increasing demand for capability and capacity to manufacture highly potent APIs (HPAPIs), particularly for contract manufacturing organizations (CMOs).

A significant proportion of HPAPIs are in the oncology field, and as approximately one-third of all new drug approvals are currently cancer medicines, this represents a substantial market opportunity. Other therapeutic areas where drugs may be highly potent include asthma and pain management.

The chemistry to make these molecules is not necessarily difficult; however, the greater challenge is in the handling and containment of them to ensure operator and environmental safety. It is vital that a careful assessment is made of the hazards posed by each individual product, reagent, and intermediate involved in the synthesis ahead of manufacture. If the risks are underestimated, people within and around the plant will be in danger. Conversely, if the risks are overestimated, the result will be excessive amounts of money spent on containment and an increase in project costs.

A compound is deemed to be potent in pharmaceutical terms if it has an eight-hour, time-weighted average occupational exposure limit (OEL) of 10 µg/m^3 or less. There is, however, no formally agreed definition of the OEL level that constitutes a "highly potent" compound. To add to the confusion, the same compound might be classified differently by individual risk assessors. This variability in classification is exemplified by a study carried out by Cambrex in which a panel of 38 molecules was sent to three risk assessors. Three different results were provided: one assessor deemed five of the 38 to be highly potent, one assessed 37 of the 38 to be highly potent, and the third fell somewhere between the two extremes.

The subjective nature of these results highlights that any CMO managing a facility to manufacture multiple APIs that may, or may not, be highly potent should consider each project on a case-by-case basis. A flexible approach allows manufacturing techniques, equipment, and containment options to be tailored to the molecule's properties, and the requirements of each individual step of the synthesis. The result should be increased safety, lower costs, and enhanced capacity for the manufacturing of HPAPIs.

Risk determination

When determining risk, the starting point is the OEL and other safety-related properties of the molecule determined as part of the drug development process. Once an investigational drug reaches the large-scale manufacturing stage, extensive safety data will have been compiled, including results from preclinical toxicology assessments, animal studies, and early-stage clinical trials.

These data on potential hazards and dose–response effects are used as a basis by experts in risk assessment to generate OELs and occupational exposure bands (OEBs) that allow informed decisions to be made about engineering strategies and industrial hygiene requirements. Appropriate containment and personal protective equipment should be supplemented by comprehensive training to ensure their proper use.

There is an important caveat. Although toxicological data offer a useful starting point, there is a difference between potency and toxicity. Potency is a measure of how much of the API is required to have a therapeutic effect; toxicity is a measure of its adverse effects. A cytotoxic drug to treat cancer may be extremely toxic but its potency might be low, and therefore, side-effects are likely. Conversely, for some drugs that only require very small doses to have a medical benefit, the dose that causes side-effects may be substantially larger.

Figure 1: Points of departure. NOEL is no-observed-effect level; NOAEL is no-adverse-event level; LOEL is low-effect level; LOAEL is low-adverse-effect level; MTD is maximum tolerated dose; BMDL is benchmark dose level; LD50 is median lethal dose; ED50 is median effective dose; and TD50 is median toxic dose.

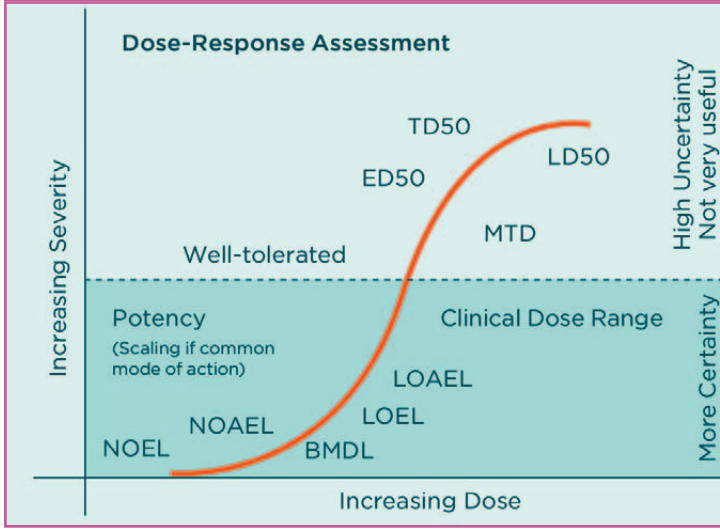


Table I: Contributors to uncertainty.

Area of uncertainty	Uncertainty factors
Intraspecies variation	10
Interspecies variability	2–12
Study duration	3–10
Low-effect level (LOEL) to low-adverse-effect level (LOAEL)	10
Database sufficiency	1–10
Severity of effect	1–10
Bioavailability	1–10
Bioaccumulation	1–10
Pharmacokinetics	3–10
Route-to-route	3–10

Modifying factors
Slope of dose-response curve
Choice of critical effect
Susceptible subpopulations
Clinical significance of critical effect
Reversibility of critical effect
Relevance of critical effect on workers
Read-across similarity
Lack of independence for uncertainty factors

The handling requirements in the manufacturing plant will be very different for the two.

Toxicology data gleaned from preclinical research or clinical trials are not designed for direct application to OELs, either. The aim of an early-phase clinical study is to determine optimal doses, balancing therapeutic benefit and what patients can tolerate. There is a huge difference between exposure in this context, and the inadvertent inhalation of dust in a manufacturing facility; there is no direct correlation between these clinical trial data and the safe exposure level for operators.

The data will, however, provide indications to issues that might occur with acute exposure. If they highlight issues such as respiratory problems, lachrymatory issues, adrenergic concerns, or somnolence, for example, acute problems might be anticipated in manufacture. There may be indicators toward chronic exposure issues, also, if there are indications that the compound might be carcinogenic, mutagenic, a sensitizer, or a clastogen.

With this information in hand, the next step is to identify any critical effects that exposure might have, such as target organ toxicity or pharmacological effect, and the dose-response curve. However, inter-person variation makes it difficult to make a definitive risk assessment.

At the lower end of the dose–response curve (**Figure 1**) is no-observed-effect level (NOEL), where the chemical causes no effect at all. The next point moving up the curve is the no-adverse-event level (NOAEL), which is commonly cited in risk assessments. Next, there are the analogous low-effect level (LOEL) and low-adverse-effect level (LOAEL), and then doses that are well tolerated, followed by the maximum tolerated dose (MTD). Past this point, the APIs are likely to be hazardous. In animal tests, at the ED50 point, half of the animals will experience an effect; at the TD50 point, half will experience toxicity; and at the LD50 point, half the study animals will die at that level of exposure.

The OEL equation (**Equation 1**) includes uncertainty factors (**Table I**) that compensate for unknowns. The numerator comprises factors that will increase occupational exposure, while the denominator includes those that will reduce it, including uncertainty factors. Those components that can contribute to uncertainty include variation between species and between subjects, the duration of the study, the severity of the effect, bioavailability and bioaccumulation, and pharmacokinetics.

FIGURE COURTESY OF THE AUTHOR

$$\text{OEL } (\mu g/m^3) = \frac{\text{PoD x BW}}{\text{UFc X MF x V}} \quad \text{[Eq. 1]}$$

Where:
OEL is occupational exposure limit
PoD is point of departure for extrapolation (mg/kg-bw/day)
BW is body weight (kg)
UFc is composite uncertainty factor
MF is modifying factor
V is volume of air breathed during work shift (m^3)

Modifying factors are also considered by some risk assessors, including the slope of the dose–response curve, and the choice of critical effect and its clinical significance, its reversibility, and its relevance to workers. Susceptible subpopulations and read-across similarity may also be considered, as may a lack of independence for uncertainty factors.

This uncertainty is at the root of the variability in risk assessments. Depending on the magnitude of uncertainty values that are applied, and whether modifying factors are given weight, there is the potential for as much as eight orders of magnitude of difference in the OEL determined by individual assessors. Reconciling this variability in the final risk assessment is a major challenge.

The solution lies, at least in part, in applying real-world context to the uncertainty factors. Perhaps the most important is the acceptable exposure risk for an individual operator, and even for the most conservative risk assessor, a one-in-one-thousand risk may well be more realistic than the one-in-one-million risk to be an appropriate likelihood of an exposure happening. The one-in-one-thousand risk is not without context: it is commonly cited as the chance of a severe injury in a hazardous work environment.

Three orders of magnitude difference in acceptable exposure risk can represent a major difference in cost. If an API is placed in a higher OEB in the absence of data and with a large weight placed on uncertainty factors, then far more costly containment will have to be employed, and the manufacturing process will take longer. How necessary is it that the API is treated as so much more hazardous? And what about the intermediates involved in its production? It is less likely that there will be a calculated OEL for those intermediates.

It is important to carefully consider exposure modifiers. Is the process likely to generate dust? If so, the likelihood of airborne hazard is far greater. How long will the operator be exposed to the material? Theoretical OELs are based on an eight-hour exposure; however, the time of potential exposure may be only a few minutes. A case-by-case assessment of the actual facility, process, and procedures will give a far more realistic picture of the hazard. There may be limits on how long people can work on individual projects because of the potential for chronic effects. If an API is a known teratogen, it may be advisable for pregnant women to keep well away.

Determining OEBs

Occupational exposure bands are a useful tool for matching a hazard with containment requirements. APIs that fall into OEB1 are non-toxic, and a standard exposure level of 500 $\mu g/m^3$ will suffice. OEB2 compounds will have special hazards, such as carcinogenicity, and the OEL will need to be lower.

At OEB3, where the hazards are greater but not extreme, the opportunity to customize handling to account for real-world situations is greater; this is where the greatest cost and time savings might be anticipated. Here, the containment could—and should—be designed around the process itself. The existing plant may suffice; alternatively, safety requirements might be met by introducing high-efficiency particulate air (HEPA) filters or soft-sided isolators, a more conservative approach than simply using personal protective equipment. The risk assessment should also consider the solvents and whether they can degrade processing or containment equipment. A programme of surrogate testing is required to prove that the containment strategy is appropriate and working successfully before the hazardous material is introduced.

OEB4 APIs are more highly potent and toxic, and special handling and careful containment will be required. An additional band, OEB4+, encompasses compounds that are so potent that their OEL falls below 0.1 $\mu g/m^3$. For OEB4 and OEB4+ compounds, the opportunity for customization is limited, and the process must be designed around the containment, and not the other way around. Dedicated isolators will most likely be employed, and rapid transfer ports for APIs deemed to be OEB4+.

This type of complete containment is extremely expensive, and while the conservative approach would be to use such containment for all highly potent compounds, in reality it may be overkill for OEB3 APIs. Instead, it may be more realistic to start out with the assumption that full containment is required, but then relax the handling requirements as further data become available, if the data suggest this will be safe. This level of flexibility will allow a CMO to offer its customers a more cost-effective solution, and faster timelines. **PTE**

Catalent and Cambrex Announce Acquisitions

Catalent announced on 3 July 2018 that it has agreed to acquire Juniper Pharmaceuticals, Inc., including its Nottingham, UK-based Juniper Pharma Services division, expanding the company's formulation development, bioavailability, and clinical-scale oral dose manufacturing services. Juniper provides bioavailability enhancement for poorly soluble compounds, including nano-milling, spray drying, hot-melt extrusion, lipid-based drug delivery, as well as cGMP clinical manufacturing for potent and controlled substances.

On 23 July 2018, Cambrex announced it has entered into an agreement to acquire dosage form contract development and manufacturing organization (CDMO) Halo Pharma, brining Cambrex into the finished dosage form CDMO market. Halo provides drug product development and commercial manufacturing services, for oral solids, liquids, creams, and sterile and non-sterile ointments, specializing in highly complex and difficult-to-produce formulations, products for paediatric indications, and controlled substances.

—*The editors of* Pharmaceutical Technology Europe

Paving the Way for Modernized Drug-Product Manufacturing Through Excipients

Commonly referred to as the future of advanced pharmaceutical manufacturing, continuous manufacturing has gained major traction in the past 10 years to enable significant improvements in efficiency, safety, cost, and speed to market.

Amina Faham is global associate director, Pharma Application Development & Innovation; **Kathryn Hewlett** is an Application Development & Innovation scientist; and **True Rogers** is R&D Technologies leader—all at The Dow Chemical Company.

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 tabletting is a form of continuous manufacturing that can eliminate expensive and energy-intensive granulation steps to offer a cost-effective solution. In addition, using less process steps removes potential sources of variability in the final drug product.

As demonstrated in **Table I**, switching to continuous processes that enable direct-compression tabletting 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 and enabling real-time release. It offers the additional benefit of smaller, more flexible manufacturing footprints that are more easily transferrable across manufacturing sites.

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

Specialty expertise in highly potent APIs

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Table I: High-shear wet granulation vs. direct compression—operating costs estimates.

		High-shear wet granulation	Direct compression
	Cost/hour	hours	hours
Equipment preparation	US$150	3	1
Material dispensing	US$120	3	3
Excipient blend	US$160	1	1
Lubrication blend	US$160	0.5	0.5
High-shear granulation	US$240	1	0
Drying the granulation	US$240	1	0
Granulation sizing	US$120	1	0
Clean-up costs	US$120	5	1
Total hours		15.5	6.5
Operating costs/1 mm—tablet batch		**€1918 (US$2250)**	**€742 (US$870)**
Savings		**~60%***	

Table II: Reduction in environmental impact of wet granulation for a single formulation.

	Wet-granulation operations	
Manufacturing capacity (10^6 tablets/year)	Water consumption (metric tons/year)	Drying energy (megawatt hour/year)
30	4	2
50	6	4
100	13	8
200	25	15
400	50	31

Assumptions: 500 mg tablets, 0.25 g Water/ 1 g dry powder, drying to 2% water content, $\Delta HVAPOR = 2257$ kJ/kg water.

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 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 pharmacopoeia 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.

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API in Capsule — *contin. from page s12*

DPI applications. Micro-dosing can be used for DPI programmes 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. **PTE**

Selecting Excipients for Liquid-Filled Hard Capsules

Thixotropic gels, thermosoftened systems, and self-emulsifying systems have expanded the range of potential excipients.

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Liquid-filled hard capsules (LFHCs) are typically composed of a shell of gelatin or hydroxypropyl methylcellulose (HPMC) and filled with compatible liquids or compositions that can flow below 70 °C. LFHC technology offers several advantages over other solid dosage forms (1). It is crucial, however, to select excipients that are compatible with capsule shell integrity and suitable for the purpose of a formulation.

Excipient considerations

Capsule shell integrity. Hard-gelatin capsules contain 13–16% moisture. Hygroscopic vehicles such as glycerin, propylene glycol, and liquid polyethylene glycols (PEGs), however, cannot be used on their own because they will cause gelatin capsule shell brittleness and fracture. If the moisture content of a filled capsule does not change more than 2% at 65% relative humidity (RH) and 25 °C for six months, then the gelatin capsule will retain its integrity. PEG 400 and 600 can also distort HPMC capsules slightly due to swelling of shell walls caused by PEG diffusion. PEG 900 does not cause this problem. HPMC capsules (moisture content 3–8%) may be useful for moisture-sensitive and hygroscopic products and whenever capsules of vegetable source need to be used (2).

Sizes of capsules. The dose of the drug substance and the quantity of an excipient that can be filled are limited by the capsule size. Commonly available hard capsule sizes for liquid filling along with their filling capacity are listed in **Table I**. Normally, only 90% of the available volume is used for ensuring proper filling of liquids and sealing of the capsules.

Viscosity. The viscosity of the filled material should be in the range of 0.1–25 Pa•s (100–25000 cps), and filling can be achieved with accuracy and precision so that coefficient of variation (CV) of fill-weight values less than 1% are often achieved. Single components such as dietary supplements (e.g., evening primrose oil) or a two-component formulation where the bioactive substance dissolves in the excipient should fill satisfactorily at ambient temperature. Capsules need sealing if the liquid is flowable at ambient temperatures. Capsule sealing machines have been improved over the years to avoid leakages (2).

The dose of the drug substance and the quantity of an excipient that can be filled are limited by the capsule size.

Cross-linking potential. Another consideration is the potential for crosslinking. A low concentration of aldehydes may be present in or produced during storage by some of the excipients used in liquid-fill formulations and may cause cross linking of gelatin, which consequently affects dissolution. To check this interaction, filled capsules are stored at 40 °C and 75% RH for six months. The capsules are emptied, cleaned, and then filled with acetaminophen as the dissolution reference material. Comparison of dissolution data for acetaminophen from the stored and reference capsules can provide evidence for interactions between the investigated fill material and the gelatin capsule. If this interaction is the problem, it can be overcome by the use of HPMC capsules that do not undergo these cross-linking reactions (3).

Excipient types

Excipients that have been found to be incompatible with hard-gelatin capsules include ethanol, glycerol, glycofurol 75, medium-chain monoglycerides (e.g., Alkoline MCM, Capmul MCM, Inwitor 308), PEG with a molecular weight (MW) less than 4000, Pharmasolve (N-methyl-2-pyrolidone), propylene glycol, Span 80, and Transcutol P (diethylene glycol monoethyl ether) (4). It may be possible, however, to incorporate

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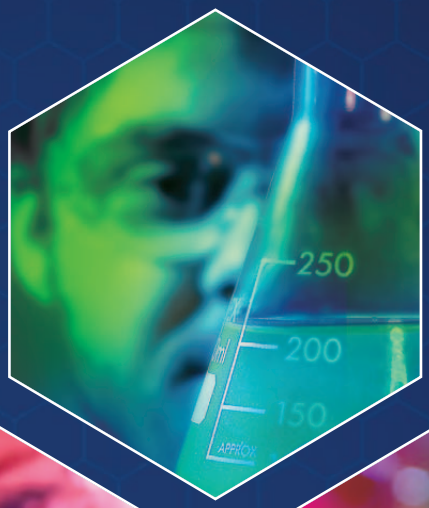

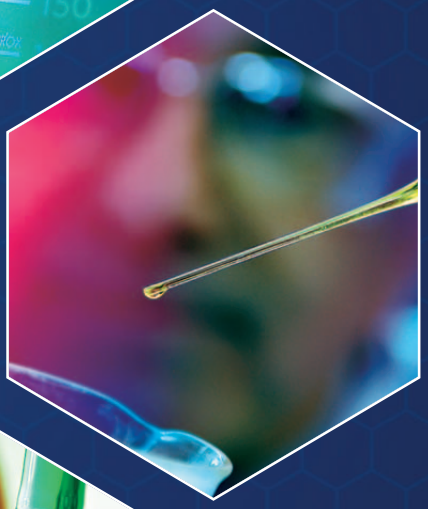

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Table I: Hard-capsule sizes and their liquid-filling capacity.

Size	00	0	1	2	3
Volume (mL)	0.91	0.68	0.5	0.37	0.30

small amounts of these excipients into liquid-fill formulations. The maximum tolerable concentration of an excipient should be determined experimentally. Formulations for hard-gelatin capsules that use mixtures containing PEG 200 have been published (5).

The numerous excipients that are compatible with hard-gelatin capsules are classified in three main categories by Cole (4) as follows:

1. Lipophilic liquids (e.g., refined oils, triglycerides, and esters)
2. Semi-solid lipophilics and viscosity modifiers (e.g., hydrogenated oils, cetostearyl/cetyl/stearyl alcohols, glyceryl esters, and Aerosil [fumed silica] for thixotropic gels)
3. Solubilizers, surfactants, emulsifiers, absorption enhancers (e.g., PEGs with MW more than 900 for HPMC capsules and more than 4000 for gelatin capsules, Tween 80, poloxamers).

Liquid filling in hard capsules

The scope of liquid filling has been increased by the use of thixotropic gels, thermosoftened systems, and self-emulsifying systems. In these semi-solid matrices (SSMs), the active substance is present as a particulate disperse phase.

Thixotropic gels. A thixotropic gel undergoes shear thinning during filling followed by gel restructuring with an increase in its apparent viscosity in the filled capsule, which reduces tendency to leak from the capsule. For example, Miglyol 95% w/w and silicon dioxide (Aerosil 200) 5% w/w mixture and a liquid paraffin 95% w/wo hydrogenated castor oil (Thixcin R) 3% w/w and Aerosil 200 2% mixture were both filled satisfactorily with a CV of fill weight of 2.8% and 2%, respectively (6). The particulate active substance is dispersed uniformly in the gel. Poloxamer/silicon dioxide gels have been also studied (7).

In another example, a highly water-soluble drug, propantheline bromide, was dispersed in Miglyol 829/Aerosil 200 thixotropic gels. The drug release rate was dependent upon the silicon dioxide concentration. An increase in Aerosil percentage increased apparent viscosity of the triglyceride gel, causing a reduction in drug diffusion from the SSM (8).

The scope of liquid filling has been increased by the use of thixotropic gels, thermosoftened systems, and self-emulsifying systems.

Thermosoftened systems. Thermosoftened formulations are prepared at an elevated temperature to produce a formulation that is sufficiently mobile for satisfactory filling. A typical formulation may be based on a solid excipient (e.g., PEG or poloxamer that will melt below 70 °C) in which the active substance will melt, dissolve, or disperse. When cooled to ambient temperature, it will be a solid or semi-solid dispersion in the capsule. The filling process temperature is usually limited up to a maximum of 70 °C to avoid thermal damage to the capsule shell and to reduce operational hazards (2). As an example, Merck's Entereg capsule, which was approved in the US in 2008, contains alvimopan suspended in PEG 3350.

As another example, a study showed that ibuprofen, which has melting point 75 °C, formed clear solutions at 70 °C with PEG 6000, 10000, poloxamer, and Dynafill (a palmitic acid derivative of polyoxyethylenepolyoxypropylene block copolymer) (9).

PEGs and poloxamers are stable for several hours at temperatures between 60 and 70 °C that are commonly used for liquid-filling thermosoftened SSMs. PEGs of MW 4000–10000 and poloxamers have ideal physical properties for liquid-filling into hard capsules by the thermosoftening process, provided that aging does not adversely affect drug-release properties (2).

Drug release from the SSM formulation could be altered by changing the hydrophilic-lipophilic balance of PEG stearate, the type and concentration of polymer, and the drug loading. This work led to a patent for Opticaps (10).

Self-emulsifying systems. This type of formulation is designed to self-emulsify in contact with aqueous media to form a fine dispersion. In each case, the basis of the formulation is a mixture of oil, a surfactant, and a co-surfactant, which can lead to improved drug delivery and bioavailability. A self-emulsifying drug delivery system (SEDDS) was formulated for Coenzyme Q10 using Myvacet 9-45 (diacetylated monoglyceride) (40% w/w) as oil, Lebrasol (50%) w/w) as surfactant, and lauroglycol 10% w/w as co-surfactant. It showed a two-fold increase in bioavailability compared to a powder formulation, when tested in dogs. A self-nanoemulsified system (SNEDDS) based on a mixture of an essential oil, polyoxol 35 castor oil (Cremophor EL), and a medium-chain mono- and diglyceride mixture (Capmul MCM-C8) overcame some of the problems, such as low solubility and irreversible precipitation of active drug, associated with the SEDDS formulations (11).

Applications of LFHC for particular drug formulations

Hygroscopic drugs. Vancomycin HCl is a highly hygroscopic drug, and it was first available only as a dry powder in sealed ampoules. The problem of hygroscopicity was solved using an SSM formulation (12). The SSM formulation was prepared by a thermosoftening technique with PEG 6000 that protected the drug from moisture uptake and produced a stable and effective preparation in a liquid-filled hard-gelatin capsule. A similar approach was used to solve a problem with the hygroscopic and very unpalatable drug mercaptamine hydrochloride (13). An SSM formulation with PEG 6000 protected the drug from moisture uptake

and masked the taste and smell of mercaptamine hydrochloride, which resulted in excellent compliance and the successful treatment of cystinosis in the children (2).

Sustained release. Sustained-release formulations have been prepared by using excipients that influence the hydrophilic-lipophilic balance of the SSM (2). Phenylpropanolamine was formulated as an SSM of arachis oil, beeswax, and silicon dioxide (14), and captopril is an SSM consisting of soybean oil and glycerol monostearate (15).

Micronization of the drugs in oil and filling the suspension in oil will minimize exposure to the potent drug.

Propranolol capsules contained a rapid-release phase of propranolol in oleic acid and a sustained-release phase of an erodible matrix of the same drug. The mixing of two phases was prevented by either inserting a hydrophilic Gelucire barrier between the two phases or by adding a hydrophobic Gelucire to the rapid-release phase to solidify it at temperatures less than 37 ºC (16). For example, isosorbide dinitrate retard capsules (Tillotts Pharma) contain 40% lactose and 60% Gelucire 50/02 as excipients.

Potent drugs. Micronization of the drugs in oil and filling the suspension in oil will minimize exposure to the potent drug. Agglomeration results in reduced solubility and hence reduced bioavailability, but filling the oily suspension instead of powder reduce the chances of agglomeration. Triamterene dosed at 20 mcg in a PEG mixture as a semi-solid filled in capsules shows a standard variation at 1.8%, compared to 3.1% for powder-fill capsules. The main reason for the improved standard deviation lies in volumetric filling, which does not show differences in density and homogeneity for semi-solids as it does for powders (17). The highest *in-vitro* dissolution was when it was formulated with PEG 1000 and Gelucire 44/14; it was lower with PEG 1500 and lowest with PEG 6000 and PEG 4000 (18).

Bioavailability enhancement. Biphenyl dimethyl dicarboxylate dissolved in a concentrate prepared from Tween 80, Neobee M-5, and triacetin provided improved bioavailability (19). Isotretinoin in sorbitan monooleate, soyabean oil, and stearoylpolyoxyl glycerides is approved as 505(b) (2) product against a softgel product (20). Another marketed product contains hydrogenated soyabean oil, polysorbate 80, soyabean oil, and white wax.

Avoiding hepatic metabolic pathway for higher bioavailability. The undecanoate ester of testosterone exhibits much lower aqueous solubility than the native form, yet demonstrates higher oral bioavailability due to a greater lipophilicity and a greater propensity to enter the systemic circulation via the lymph, particularly when formulated as a lipid solution (Andriol Testocaps). It is dissolved in castor oil and propylene glycol monolaurate and filled as a soft-gelatin capsule (21) or LFHC.

Formulating drug compounds in liquid or semi-solid excipients is used to target lymphatic transport (22) or to circumvent the impact of transporters (23) and metabolizing enzymes (24) in the gastrointestinal tract.

Abuse-resistant formulations. Liquid and semisolid filled capsules by their nature are resistant to crushing and powdering, and a drug is difficult to extract from waxes. For example, Oradur (Durect) uses a high-viscosity base matrix of sucrose acetate isobutrate.

Conclusion

Large varieties of excipients are available for use in LFHCs based on the purpose of the formulation. Compatibility with the capsule shell and viscosity at the temperature of filling up to 70 ºC are most important considerations. With the advancements in machinery for sealing of hard capsules, more products could be developed as LFHCs.

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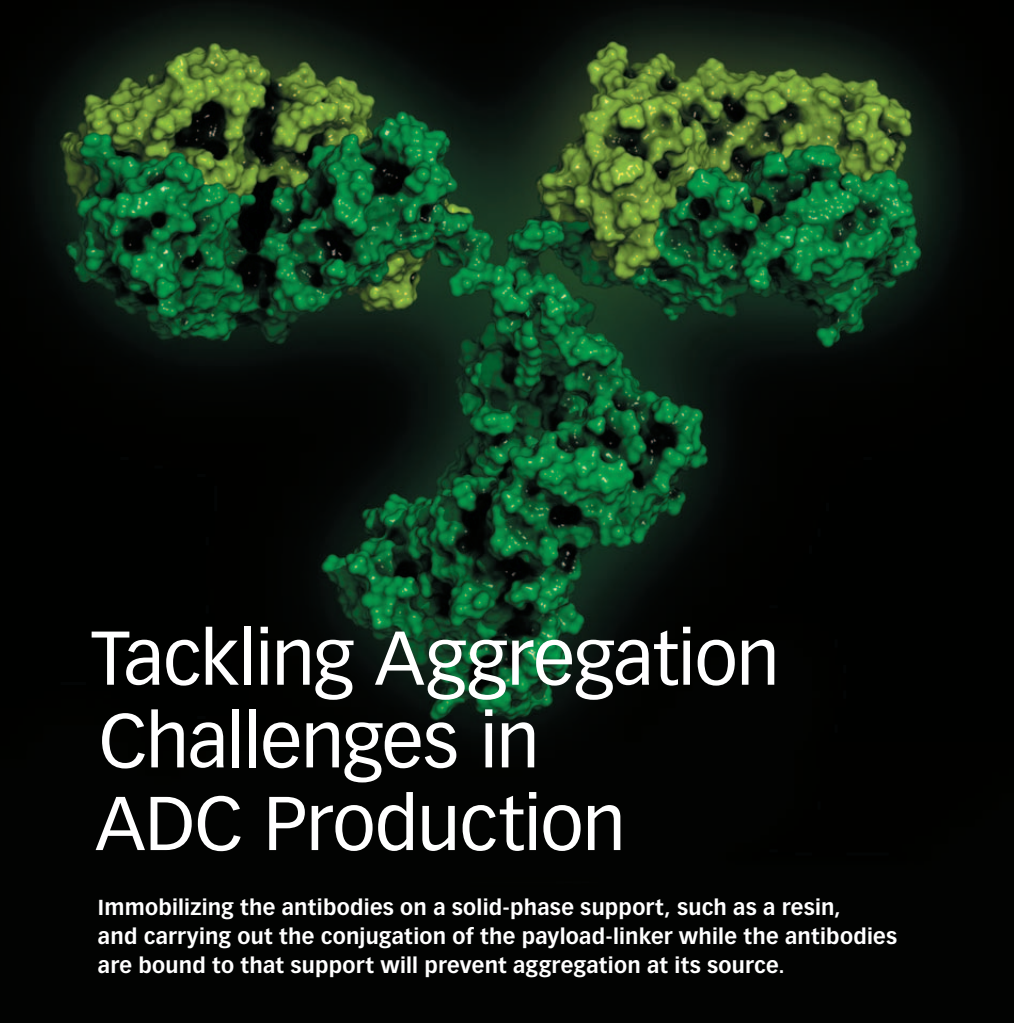

Tackling Aggregation Challenges in ADC Production

Immobilizing the antibodies on a solid-phase support, such as a resin, and carrying out the conjugation of the payload-linker while the antibodies are bound to that support will prevent aggregation at its source.

Adeline Siew, PhD

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 Europe* 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

PTE: 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:

- Unfavourable 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.

"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."—*Johnson*

Conventional techniques

PTE: 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

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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.

> **"The best solution to the aggregation problems prevalent with conventional conjugation methodology is to prevent aggregation at its source."—*Johnson***

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 immunogenic 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

PTE: 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 'unfavourable' 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)…"—*Johnson***

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

PTE: 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 favoured 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 as 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. **PTE**

Robotics Solve Aseptic Filling Challenges

Automated robotic arms manipulate nested trays and containers inside closed aseptic filling systems.

Jennifer Markarian

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 because 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 re-work [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. Procyshyn 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."

Procyshyn 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 Procyshyn. 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 23 May 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.

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.

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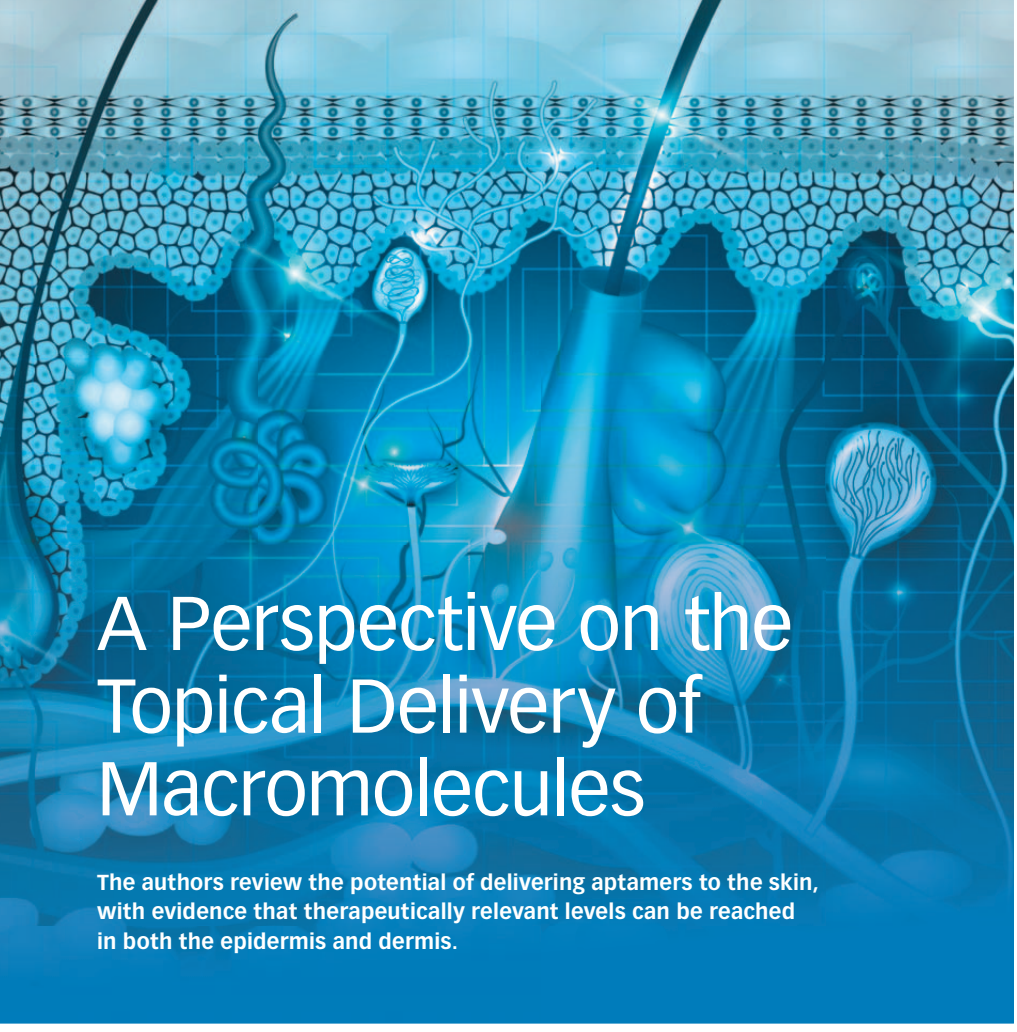


A Perspective on the Topical Delivery of Macromolecules

The authors review the potential of delivering aptamers to the skin, with evidence that therapeutically relevant levels can be reached in both the epidermis and dermis.

Marc Brown, PhD, is chief scientific officer and co-founder of MedPharm; and **Jon Lenn, PhD,** is senior vice-president for MedPharm's US operations.

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.

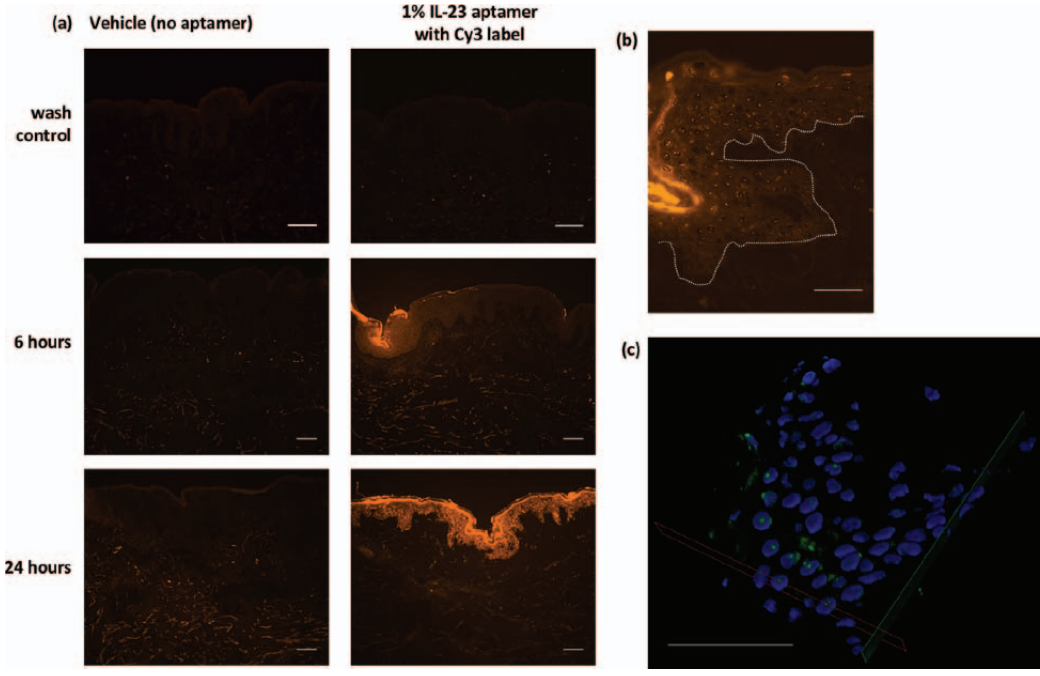
Topical delivery of macromolecules

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 rodents 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.

At present, there is no approved topical formulation containing a drug with a molecular weight of more than 1000 Da.

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).

Figure 1: Topical application of IL-23 aptamer shows penetration into the human skin and into the keratinocytes. (a) Penetration of IL-23 Cy3 labelled aptamer (orange) into intact human abdominal skin after zero (wash control), 6 and 24 hours post dosing. (b) Uptake of IL-23 aptamer into skin keratinocytes (dashed lines indicating the epidermal junction). (c) Intracellular uptake of aptamer (green) with nuclear DAPI stain (blue) used for cellular orientation. Scale bar = 50 µm.



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 potential topical treatment for atopic dermatitis. The product progressed as Avrina into Phase I/II (14) but despite the clinically positive data, it does not seem to have progressed further. Some of the constraints related to modifications of antisense molecules and their fixed structural nature may explain this lack of progression. More recently, topical application of a tumor necrosis factor (TNF)-α suppressing antisense spherical nucleic acid showed that treatment with the highest dose resulted in a statistically significant decrease in TNF messenger ribonucleic acid (mRNA) expression in psoriatic skin (15). This technology will be interesting to watch because it appears there are several similar compounds in early development.

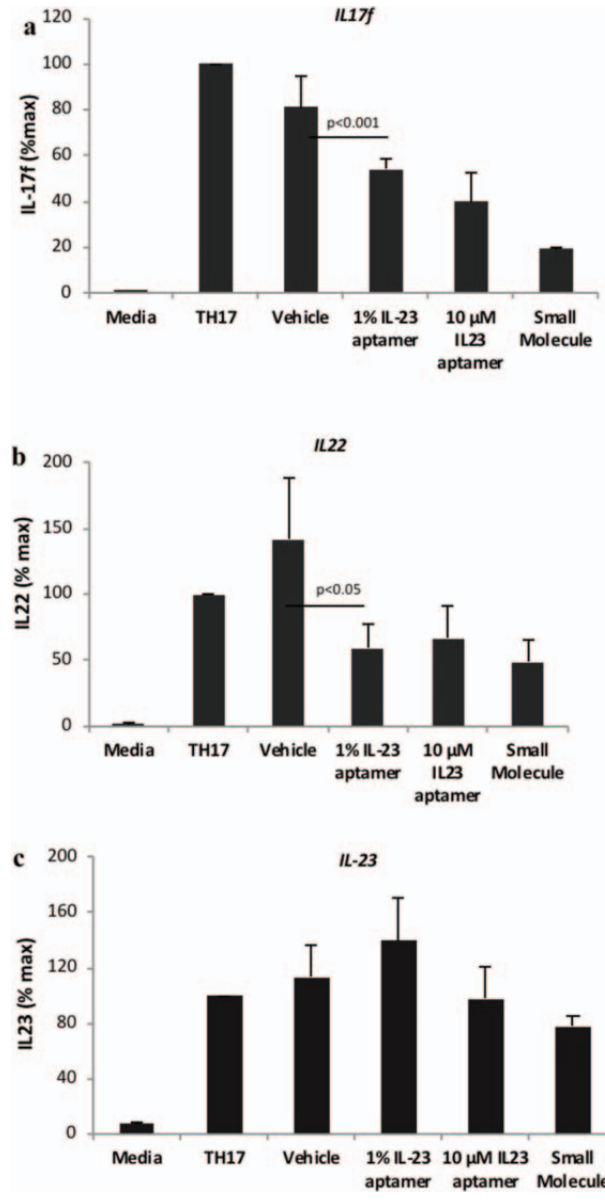
One of the challenges when attempting to understand passive topical delivery of compounds is establishing a model or testing system that mimics the *in-vivo* condition.

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

Figures are courtesy of the authors.

Figure 2: Topical application of IL-23 aptamer inhibits Th17- and IL 22-derived cytokines in human skin. Freshly excised human abdominal skin was mounted and clamped in place using static cells containing growth media and stimulated 24 hours later to induce a Th17 response. The skin was treated topically twice with 8 µL of IL-23 aptamer (210 µg/cm²) in an aqueous vehicle before and concurrent with Th17 stimulation. IL-23 aptamer (10 µM) and a ROR gamma inverse agonist (10 µM; small molecule) was included in the media as systemic controls. Twenty-four hours post stimulation, skin was harvested and relative transcript levels of Th17-type cytokines, IL-17f (a), IL-22 (b), and IL-23 (c) were determined by quantitative polymerase chain reaction (qPCR). Bars represent the mean percent of maximum stimulation (set to 100%) from three different skin donors (n=3).



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

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was 40 times larger than what is commonly accepted as possible for passive topical delivery in the skin.

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.

In the study, the authors used multiple approaches to demonstrate the topical delivery of the aptamers, including fluorescently labelled aptamer, confocal microscopy, and a novel dual hybridization assay that used capture and detection 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.

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.

Aptamers represent a new class of molecules that could have antibody-like binding affinity with the possibility of topical delivery.

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 programme, 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.

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Testing Topicals: Analytical Strategies for the *In Vitro* Demonstration of Bioequivalence

Taking acyclovir as an illustration, this article examines IVBE testing requirements for topical creams and explores some of the analytical techniques necessary.

Paul Kippax is director of Product Management–Morphology Group; **Jennifer Burt** is applications specialist; and **Carolyn O'Grady** is UK applications manager, all at Malvern Panalytical.

Topical pharmaceutical products usually take the form of lotions, creams, gels, ointments, or pastes and are used to deliver locally-acting drugs to their sites of action. Local anesthetics, dermatological treatments for eczema and dermatitis, and antiviral preparations for cold sores are just some of the medications delivered using formulations applied directly to the skin. As many locally acting drugs are deemed to have complex delivery routes, they fall within the growing pharmaceutical category of complex drug products. Complex drug products include drugs with complex active ingredients or formulations and those such as inhalers and nasal sprays, which rely on specific drug-device combinations. The generic versions of complex drug products are in high demand (1), and pressure is mounting to develop these alternatives more quickly and more efficiently.

One challenge in developing a generic version of a locally acting drug lies in demonstrating its bioequivalence (BE) to its reference-listed drug (RLD) counterpart. For solid oral-dose formulations intended for systemic delivery, this is an established process involving human pharmacokinetic (PK) studies supported by *in-vitro* dissolution testing. PK studies based on the systemic *in vivo* attainment of a therapeutically active drug concentration, however, have limited relevance for locally acting substances. Measuring directly at the site of action also presents challenges, given the potential variability of factors such as exposure time and size of application area. Alternative approaches are, therefore, being explored and are exemplified in US Food and Drug Administration (FDA) guidance on establishing bioequivalence for acyclovir (2), the API in the topical cold sore treatment Zovirax (GlaxoSmithKline). *In-vitro* bioequivalence (IVBE) testing is one of the options proposed. Taking acyclovir as an illustration, this article examines IVBE testing requirements for topical creams and explores some of the analytical techniques necessary.

Complex generics and the regulatory landscape

A whitepaper (3) arising from a 2016 conference at the New York Academy of Sciences (4) divides complex drugs into two categories, based on the challenges involved in proving their pharmaceutical equivalence (PE) and BE. The first category includes those products with complex active ingredients and/or complex formulations, for which the demonstration of both PE and BE is difficult. The second category includes products for which delivery routes, dosage forms, or drug-device combinations are complex, and the establishment of either PE or BE is challenging. Because of their delivery route and the difficulties of assessing BE, locally acting topical drugs fall into this second group.

As discussed, for topical, locally acting drugs, systemic PK testing is not always relevant or easily conducted. Therefore, most require clinical endpoint studies to determine BE. However, these studies are costly, time-intensive, and require high patient numbers, creating a barrier to entry for development of generic formulations. Innovators needing to demonstrate batch-to-batch equivalence for post-approval changes or scale-up face a similar challenge (5). In recognition of this, FDA has issued various product-specific guidance documents for complex drug products, including some locally- acting drugs such as cyclosporine ophthalmic emulsions (6) and acyclovir ointments (7). These guidance documents include simplified product-specific BE recommendations and are published on a case-by-case basis. Importantly, they include the use of *in-vitro* methods to assess bioequivalence, thereby linking the physical and chemical properties of a drug with its efficacy. For locally acting topical drugs, IVBE is restricted to formulations that have qualitative (Q1) and quantitative (Q2) equivalence to the RLD. The availability of suitable analytical techniques, a thorough evaluation and understanding of the reference drug, and identification

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of the critical process parameters are all necessary precursors to successful implementation of this approach for the development of generics and the reduction of the need for clinical endpoint studies.

Deformulation and bioequivalence

Applying physicochemical characterization methods to the development of pharmaceutical generics is not a new concept, and the now-familiar deformulation workflow for solid-dosage forms was first published in 2005 (8). Fundamental to this is the concept that having quantitative and qualitative information about key RLD ingredients simplifies the optimization of prototype formulations, reducing both the number of experiments needed and the risks along the developmental pathway.

This application of physicochemical methods to deformulation can also be used directly in the development of complex generic drugs. FDA sets out three levels of equivalence requirements. Q1 equivalence asks if there is qualitative similarity between the RLD and test (generic) drug product: do they have the same active ingredient and excipients? Q2 equivalence asks if the active and excipient ingredients are present in the same amounts in both products. Q3 equivalence examines whether both the RLD and the test product have the same physicochemical attributes or microstructure. Similarity at the Q3 level delivers the opportunity to move to *in-vitro* bioequivalence testing and provides the possibility of approval without clinical endpoint studies (9). Not only does this offer considerable cost savings, but potentially a faster time to market. Different Q3 parameters being considered in product-specific guidance documents include: appearance, pH, globule size distribution, rheological behaviour, drug release profile, drug particle size distribution, drug polymorphic form, and specific gravity (10). Choosing the correct analytical techniques to measure these parameters and applying them effectively can significantly reduce the time, cost, and risk involved in developing a complex generic product.

Acyclovir and FDA guidance for the development of generic versions

Acyclovir was the world's first successful antiviral drug and has been available in topical form since the early 1980s, with oral and intravenous preparations also prescribed for systemic use. Although marketed originally and still available as Zovirax since its patent expiration in the 1990s, acyclovir has been available under many brand names worldwide. The drug treats viruses of the herpes family, most notably herpes simplex (HSV) Types 1 and 2 (cold sores and genital herpes) and Varicella-zoster virus (chickenpox and shingles). The topical formulation is marketed primarily as a cold sore treatment.

FDA guidance covering topical acyclovir (2) defines the criteria that must be met for formulations to qualify as suitable for IVBE studies. Key among these is that the "test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization" (2). More specifically, testing should include the following:

- Assessment of appearance
- Analysis of the acyclovir polymorphic form in the drug product
- Analysis of particle size distribution and crystal habit with representative microscopic images at multiple magnifications
- Analysis of the rheological behaviour, which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behaviour of semi-solid dosage forms
- Analysis of specific gravity, water activity, pH, and any other potentially relevant physical and structural similarity characterizations.

The following case studies illustrate the use of morphological imaging, including Morphologically-Directed Raman Spectroscopy (MDRS) and rheological measurements in the physicochemical characterization of acyclovir cream, and discuss the insight they offer. Specifically, these case studies look at a comparison of an innovator product and a generic version.

Case study: Particle size and shape of the generic and innovator products

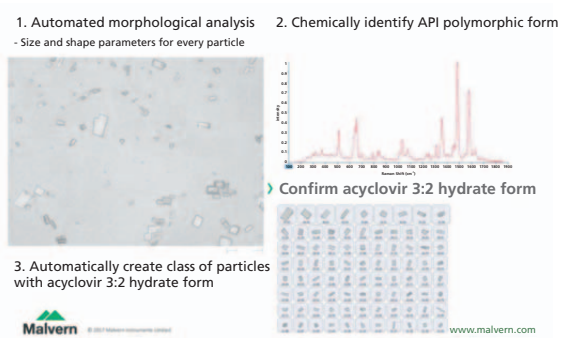
Many drug substances exist in more than one crystal form. Such polymorphism can affect a drug's chemical and physical properties and influence its processing or manufacture. These variations can also affect drug product stability, dissolution, and bioavailability, with consequences for quality, safety, and efficacy. It is, therefore, vital to characterize and understand polymorphs in terms of their particle size, shape, and chemistry. In topical formulations, the particle size and crystal habit of the API will, for example, influence the speed at which it permeates the skin. *In-vitro* permeation data indicate that for acyclovir, small size rectangular crystals are more rapidly absorbed than large oval ones (11).

MDRS can be used to determine the polymorphic form of the API in a formulation, its particle size, and its crystal habit, enabling direct comparison between test products and the RLD. This technique combines automated static particle imaging with Raman spectroscopy to measure particle size and shape and provide chemical identification of individual particles, enabling the generation of component-specific size and shape distributions.

Figure 1 shows how Morphologically-Directed Raman Spectroscopy (MDRS) (Morphologi 4-ID, Malvern Panalytical) can be used to determine the polymorphic form of API particles. The instrument first conducts automated morphological analysis for all particles in the acyclovir sample, establishing particle size and shape distributions. The instrument then returns to a selected subset of the total particle population to obtain Raman spectra to identify which particles are API (the acyclovir 3:2 hydrate form).

Once particle classes have been established, MDRS can be used to determine the particle size

Figure 1: Using Morphologically-Directed Raman Spectroscopy (MDRS) to determine API polymorphic form in acyclovir cream.



distribution (PSD) specifically for the API (**Figure 2**). In this case, comparing PSDs for the API in the innovator (blue) and generic (red) preparations shows that the API particles in the generic formulation are smaller than those in the innovator. This would be expected to have a significant impact on the solubility rate of the API and, therefore, its bioavailability.

Figure 3 shows a comparison of particle shape distributions, using both circularity (left) and elongation (right) parameters. The API present in the generic (red) is more circular and less elongated than that in the innovator (blue), which contains more-rectangular API particles. This difference may suggest that, although both formulations contain a similar polymorph, the processing of the generic formulation has led to particle attrition (crystal breakage). This may also explain the differences in particle size.

Case study: Rheological parameters

As a complex formulation, acyclovir cream typically consists of a base comprising an oil-wax phase (e.g., liquid paraffin, white soft paraffin, and silicone oils), stabilizers, and thickening agents, into which go the API and preservatives, together with additives to improve sensory or functional behaviour. Formulation, composition, and processing of the cream all impact its underlying microstructure (droplet volume and size and lamellar structure), in turn influencing the final product's rheological behaviour, evident in such characteristics as flow and deformation. Understanding the rheology of a product is essential in controlling and optimizing the physical properties that deliver the appropriate stability, texture, delivery, and appearance. Rheology is therefore a crucial link between formulation, processing, and final product performance, and measuring a range of rheological parameters provides the information needed to engineer a product's microstructure toward the desired end-product properties.

FDA guidance on Q3 testing of acyclovir topical creams recommends the following in respect of rheological measurements (2):

- A complete flow curve of shear stress (or viscosity) vs. shear rate should consist of multiple data points across the range of attainable shear rates, until low- or high-shear plateaus are identified
- Yield stress values should be reported if the material tested exhibits plastic flow behaviour

Figures are courtesy of the authors

Figure 2: Using Morphologically-Directed Raman Spectroscopy (MDRS) to determine API particle size in acyclovir cream (generic formulation shown in red, and innovator in blue).

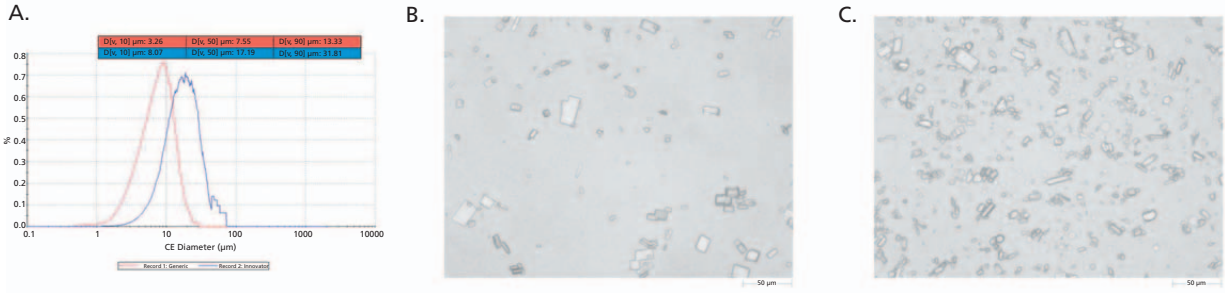
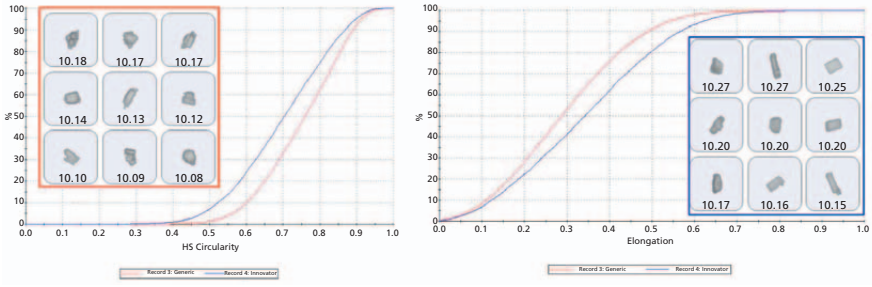


Figure 3: Using Morphologically-Directed Raman Spectroscopy (MDRS) to determine API crystal habit in acyclovir cream (generic formulation shown in red, and innovator in blue).



- The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported.

Examples for both an innovator and a generic product, with measurements made on a rotational rheometer (Kinexus, Malvern Panalytical), are discussed in the following:

Yield stress. Many emulsions behave like solids at rest, because emulsion droplets flocculate to form a floc network. The stress that must be applied to break down this structure and cause the material to flow is known as the yield stress. Generally, the higher the yield stress, the more solid-like the structure. A cream with a higher yield stress will need more force to be squeezed from a tube but will better retain its structure when applied to the skin, allowing a greater amount to stay at the desired location. The cream will also appear and feel thicker.

Measuring yield stress using a rotational rheometer involves linear ramping of shear stress over time and identifying when the viscosity of the sample starts to decrease. **Figure 4** shows measurements for the innovator (blue) and a generic (green) acyclovir product, showing that the innovator has a much higher yield stress than the generic product in this case. This structure may make the innovator product easier to apply to the area of skin requiring treatment.

Linear viscoelastic response. Viscoelastic properties are representative of the underlying microstructure of a material before it yields, and provide information on its stiffness and elasticity. Measurement involves oscillatory testing on a rotational rheometer, whereby the sample is sheared back and forth using small forces and displacement so as not to disturb the structure. In this case, an oscillation frequency of 1 Hz, generally representative of textural processes (touching), was used to test the generic and innovator products. G*, the complex shear modulus, which is a measure of total stiffness (from elasticity and viscosity combined) and the phase angle (δ), can be considered as a ratio between viscosity and elasticity and provide information about the viscoelastic properties, or springiness/stiffness of the material. The generic formulation was found to have a more elastic character, compared to the much higher G* value of the innovator, which will deform less with a given amount of force and will feel stiffer to the touch. This corresponds with the yield stress results, because a stiffer structure will require more stress to rupture. Again, the stiffer structure of the innovator product may aid patients in applying the formulation.

Viscosity versus shear rate. **Figure 5** shows viscosity as a function of shear rate for the innovator (red line in **Figure 5**) and generic (blue line in **Figure 5**) products. Both are shear-thinning, so viscosity decreases as shear rate increases, the result of microstructural reorganization. The innovator has a higher viscosity across all shear rates than the generic and is likely to flow less readily and spread less easily in use. It will also feel thicker on rubbing because of its high viscosity at high shear rates, and is likely to more readily hold its structure on application and stay in place for longer, potentially providing more effective treatment.

Conclusion

In-vitro bioequivalence is of significant interest across the generic-drug industry and is especially welcomed by those working with complex generic products, where traditional BE testing may not yield the most appropriate results. FDA bioequivalence guidance documents are now

PDA Europe Conference, Exhibition, Education

PDA
Parenteral Drug Association

Outsourcing & Supply Chain – A 360° View

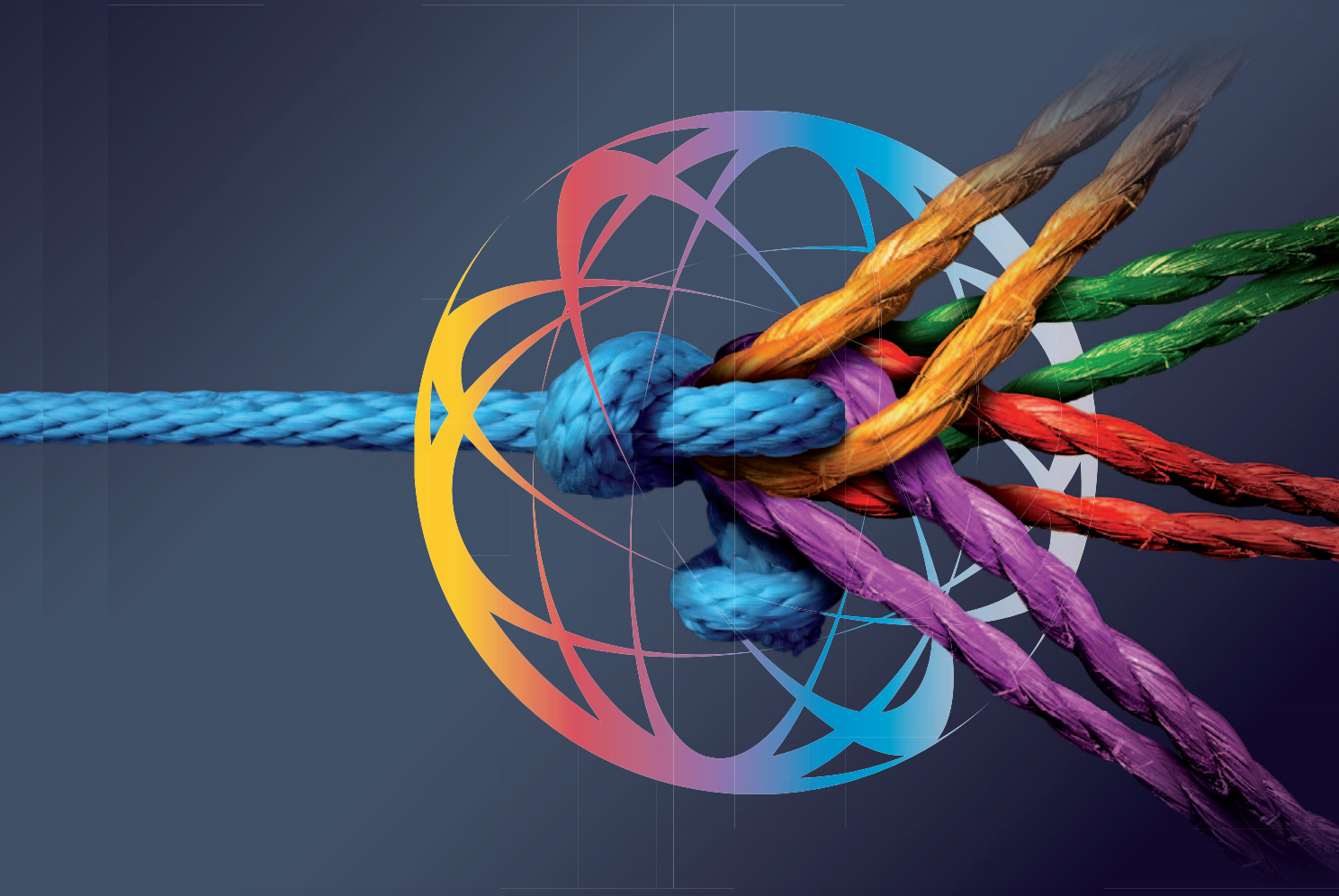


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Figure 4: Measuring yield stress in topical acyclovir creams (generic formulation shown in green, and innovator in blue).

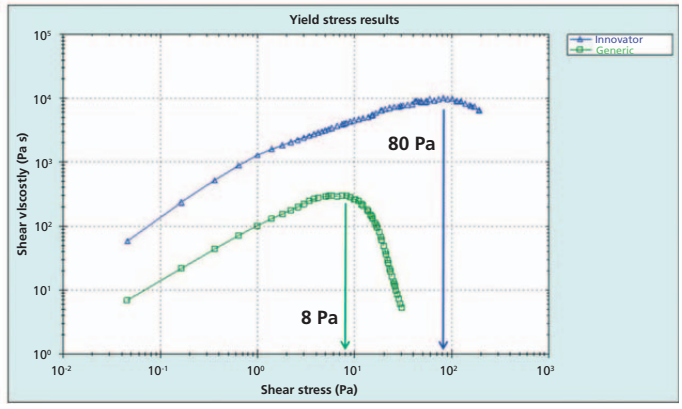
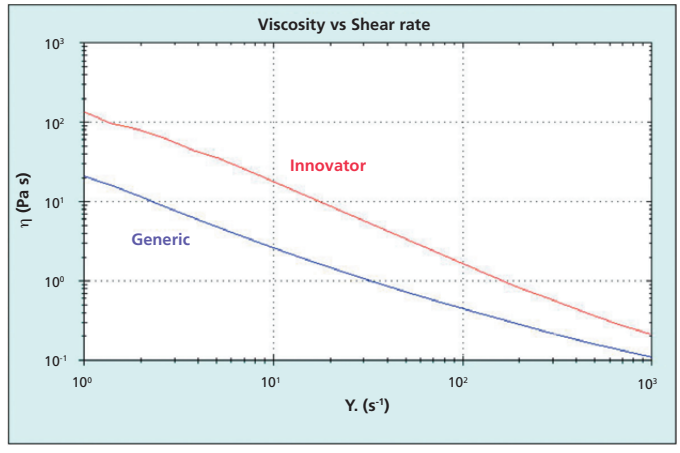


Figure 5: Viscosity vs shear rate for acyclovir creams.



available for a range of complex drug products, including various topical formulations. These documents set out in detail the Q3 physicochemical analysis required for a product to be considered for approval on the basis of IVBE testing, in place of clinical endpoint testing. Selecting the most appropriate analytical techniques for physicochemical characterization will ensure a more complete understanding of the product at both the deformulation stage of generic development, through to manufacture, quality control, and post-approval testing.

Taking acyclovir cream as an example, this article presents data generated using two key technologies: MDRS and rotational rheometry. The data illustrate the type of information required to compare the properties of innovator and generic forms and demonstrate the power of these techniques in providing real insight into topical products and their behaviours. Between these two technologies, it is possible to answer to three of the five criteria from the FDA guidance for the physicochemical (Q3) IVBE testing of generic acyclovir products (2).

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2018 PLANNING GUIDE

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

Pharmaceutical Technology Europe and CPhI are brands of UBM, a part of Informa PLC.

CPhI Worldwide 2018 Highlights

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

Comprehensive Exhibition

Tuesday, 9 October 2018: 9:30–17:30
Wednesday, 10 October 2018: 9:30–17:30
Thursday, 11 October 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 6–8 for more information.

Educational Sessions

Tuesday, 9 October–Thursday, 11 October 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** programme, company representatives explain the latest trends and technologies for API development, excipients, drug development, and manufacturing, packaging, drug delivery, contract services, and more. The Pharma Insight Keynotes and Pharma Insight Briefings are free to attend. See CPhI pages 9–12 for details.

Recognising Innovation: CPhI Pharma Awards Gala

Tuesday, 9 October 2018, 18:00–22:30
Eurostars Madrid Tower, Madrid, Spain

The CPhI Pharma Awards honour innovation and excellence in 17 categories. Winners will be announced at the CPhI Pharma Awards Gala on 9 October. For additional information, see page CPhI 13 or 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.

In a second roundtable, representatives from Country Pavilion partners will discuss key challenges regarding import and export strategy, globalization, the regulatory environment, and emerging markets.

Big Data & Machine Learning Pharma Summit

In collaboration with Innovation Enterprise
Wednesday 10 October, 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.

To register, visit: www.theinnovationenterprise.com/summits/big-data-and-machine-learning-summit-europe-2018.

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Women in Leadership Forum

Empowering Women in Pharma
Sponsored by DuPont

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

While company leaders are creating programmes to increase diversity in their organisations 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

8:00–08:30
Breakfast & Networking

8:30–08:35
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

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 27 July 2018)—View www.cphi.com/europe for schedule updates

Time	Activity	Location
Tuesday, 9 October 2018		
8:30–11:00	C-Suite Roundtable (invitation only)	IFEMA, Feria de Madrid, Room S100E
9:30–17:30	Exhibition Open	IFEMA, Feria de Madrid
10:30–17:00	Pharma Insight Keynotes and Pharma Insight Briefings	CPhI Theatre—9C80 ICSE Theatre—1G90 Innopack/P-MEC Theatre—4F121
10:30–11:40	Pharma Insight Workshops	Pharma Forum, the Avenida between Halls 5 and 6
14:00–17:30	Country Pavillion Roundtable (invitation only)	North Convention Centre, IFEMA, Feria de Madrid
Begins at 18:30	CPhI Pharma Awards Gala	Eurostars Madrid Tower, Coaches depart IFEMA at 17:30.
Wednesday, 10 October 2018		
8:30–11:30	Women in Leadership Forum	Room N106, North Convention Centre, IFEMA, Feria de Madrid
9:30–17:30	Big Data & Machine Learning Pharma Summit	Room N101, North Convention Centre, IFEMA, Feria de Madrid
9:30–17:30	Exhibition Open	IFEMA, Feria de Madrid
10:30–17:00	Pharma Insight Keynotes and Pharma Insight Briefings	CPhI Theatre—9C80 ICSE Theatre—1G90 Innopack/P-MEC Theatre—4F121
10:30–11:40 13:10–13:40	Pharma Insight Workshops	Pharma Forum, the Avenida between Halls 5 and 6
Thursday, 11 October 2018		
9:30–16:00	Exhibition Open	IFEMA, Feria de Madrid
10:30–15:40	Pharma Insight Keynotes and Pharma Insight Briefings	CPhI Theatre—9C80 ICSE Theatre—1G90 Innopack/P-MEC Theatre—4F121
10:30–11:40	Pharma Insight Workshops	Pharma Forum, the Avenida between Halls 5 and 6

Welcome to bioLIVE

Launched in 2018 and co-located with 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 within the industry. The exhibition and conference offer trade show 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 production
- Gene therapy production
- Automation systems and software
- Formulation services
- Freeze-drying
- Process control, smart lab design, cleanrooms
- Biopharma ingredients
- Contract services and R&D
- Commercialised products, vaccines, and biosimilars.

The bioLIVE exhibition will feature products and services used in the development of biopharmaceuticals. For updates, see www.bio.live.

www.bio.live

Tuesday, 9 October 2018: 9:30–17:30
Wednesday, 10 October 2018: 9:30–17:30
Thursday, 11 October 2018: 9:30–16:00
Hall 12, IFEMA, Feria de Madrid, Spain

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bioLIVE exhibiting companies, as of 18 July 2018.

Company	Country	Stand
73100	Portugal	12A20
Abzena	United States	12A26
Admescope	Finland	12A24
BIOCOM AG	Germany	12A36
BIOTECHPHARMA UAB	Liechtenstein	12B31
BSP Pharmaceuticals S.p.a	Italy	12B14
c-LEcta GmbH	Germany	12A30
China Chamber of Commerce of Medicines & Health Products	China	12A32
Dow Europe GmbH	Switzerland	12C31
Frontier Biotechnologies Inc.	Switzerland	12B11
GeneScience Pharmaceuticals Co., Ltd.	China	12A33
HORIBA	United Kingdom	12B30
Luina Bio Pty Ldt	Australia	12C30
M J Biotech Private Limited	India	12B10
MabPlex International	United States	12C12
Nanogen Pharmaceutical Biotechnology JSC	Vietnam	12D20
Prestige BioPharma Pte. Ltd.	Singapore	12A22
Rousselot Netherlands	Netherlands	12B13
Samsung Biologics	South Korea	12C14
Sekisui	United Kingdom	12C10
SINOVAC BIOTECH CO., LTD.	China	12D24

bioLIVE Conference Programming

bioLIVE offers free, comprehensive content programmes 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.

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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

Small-molecule drug companies looking to enter biologics can gather insights on how to break into the biologics sector.

Visit bio.live/content-programme for updates.

Registration

A Visitor's pass to bioLIVE provides access to all CPhI events. See page CPhI 14 for details.

bioLIVE Speakers

Confirmed speakers, as of 31 July 2018, include:

- Lucy Foley, director of biologics, 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 and marketing director, Cobra Biologics
- Paul Thorning, CEO, Crystec Pharma

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 the six co-located events—CPhI, ICSE, bioLIVE, P-MEC, FDF, and InnoPack—at CPhI Worldwide from 9–11 October 2018.

More than 2500 vendors will showcase their products and services—including APIs, excipients, equipment, packaging, finished dosage products, and contract services—for the development and manufacture of small-molecule and biologic-based 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 7 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 labelling 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, 9 October 2018: 9:30–17:30
Wednesday, 10 October 2018: 9:30–17:30
Thursday, 11 October 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 innovative 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.

bioLIVE

CPhI worldwide

iCSE FDF InnoPack P-mec

VENUE LAYOUT

09 -11 October 2018
IFEMA Feria de Madrid, Spain

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Featured Exhibitors

Be sure to visit the following companies exhibiting at CPhI Worldwide.

Abitec Corporation
www.abiteccorp.com
Stand # 8A110SSP

Beneo GmbH
www.galeniq.com
Stand # 8F90

Catalent Pharma Solutions
www.catalent.com
Stand # 3D10

Colorcon
www.colorcon.com
Stand # 8F70

Corden Pharma
www.cordenpharma.com
Stand # 7F30

Dr Paul Lohmann
www.lohmann4minerals.com
Stand # 7B80

Gerresheimer
www.gerresheimer.com
Stand # 4C30

Grifols International SA
www.partnershipgrifols.com
Stand # 3F102

Hermes Pharma
www.hermes-pharma.com
Stand # 1G41

Lonza
www.lonza.com
Stand # 3F30

Nolato
www.nolato.com
Stand # 4D22

Novasep
www.novasep.com
Stand # 10C82

Novo Nordisk
www.novonordiskpharmatech.com
Stand # 8A20

Panreac AppliChem
www.itwreagents.com
Stand # 8B101

Taiwan Pharmaceutical Alliance
www.pitdc.org.tw
Stand # 9A70

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Sessions Explore Bio/Pharma Topics

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, serivces, and product offerings.

All sessions are free to attend. Session and speaker information is as of 31 July 2018. For updates visit cphi.com/europe/agenda.

CPhI: APIs, Excipients, and Drug Delivery

KEYNOTE SESSIONS
Location: CPhI Theatre—9C80

Tuesday, 9 October 2018, 10:30–11:00
Addressing an Unmet Need: How Pharmaceutical Industry Professionals Can Extract Value from Data Routinely Collected on Products and Processes
Mike Tobyn, research fellow, Bristol-Myers Squibb

Tuesday, 9 October 2018, 11:10–11:40
Quality by Design
Amina Faham, executive board member, International Pharmaceutical Excipients Council Europe

Wednesday, 10 October 2018, 10:30–11:00
Current Trends in Generics Portfolio Strategies
Brandon Boyd, segment lead – generics, Clarivate Analytics

Wednesday, 10 October 2018, 11:10–11:40
Brexit: The Wider Implications for the Pharmaceutical Sector
In Partnership with SCI

Thursday, 11 October 2018, 10:30–11:00
The Future is Digital and What This Means for Pharma
Speaker to be announced

Thursday, 11 October 2018, 11:10–11:40
Logistics: A Point of View from Outside Pharma
Speaker to be announced

CPhI: APIs, Excipients, and Drug Delivery

PHARMA INSIGHT BRIEFINGS
Location: CPhI Theatre—9C80

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

Pharma Insight Briefings

Tuesday, 9 October 2018: 10:30–17:00
Wednesday, 10 October 2018: 10:30–17:00
Thursday, 11 October 2018: 10:30–15:40
Free to attend. Seating is limited.

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

Tuesday, 9 October 2018, 13:50–14:20
Shaken Not Stirred? How Will *USP* <661.1> and ICH Q3D Impact Your Packaging Materials Cocktail?
Dan-Ola Svensson, technical manager, Clariant Plastics & Coatings

Tuesday, 9 October 2018, 15:10–15:40
Biological Assays: Responding to Increasing Demands in the Release of Peptide-Based APIs
Michael Postlethwaite, business development manager, Bachem

Wednesday, 10 October 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, 10 October 2018, 12:30–13:00
Capsule-Based Dry Powder Inhalation: Opportunities, Trends, and Solutions
Fernando Diez, scientific business development manager, ACG Associated Capsules

Pharma Insight Workshops

Pharma Insight Theatre, Pharma Forum,
Avenida between Halls 5 and 6

Tuesday, 9 October 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 Önol, head of regulatory affairs, quality assurance and quality compliance, Boehringer Ingelheim (TBC)

Wednesday, 10 October 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, 10 October 2018, 11:10–11:40
Russia: Market Outlook
In Partnership with Association of the Russian Pharmaceutical Manufacturers

Wednesday, 10 October 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, 11 October 2018, 10:30–11:00
China: Entering the Arena of European Generics
Amit Bansal, head–global generics, Sanofi India

Thursday, 11 October 2018, 11:10–11:40
What´s the New Scenario for Biological Products and Biosimilars?
Uwe Gudat, head of clinical safety and pharmacovigilance, Fresenius Kabi SwissBioSim GmbH

Wednesday, 10 October 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

Wednesday, 10 October 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, 10 October 2018, 15:50–16:20
Superba Krill Oil Supplementation Improves Skin Hydration and Elasticity in Adults
Andreas Berg Storsve, director R&D, Aker Biomarine

ICSE: Outsourcing Formulation and Manufacturing

KEYNOTE SESSIONS
Location: ICSE Theatre—1G90

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

Tuesday, 9 October 2018, 11:10–11:40
Bioprocessing Overlap: What Small-Molecule Drug Manufacturers Can Learn from Large-Molecule Drug Manufacturers
Powered by bioLIVE

Wednesday, 10 October 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
Christoph Bieri, managing partner, Kurmann Partners AG

Thursday, 11 October 2018, 10:30–11:40
Discussion Panel: Creating an Industry 4.0 Strategy as Part of Your Manufacturing Plan to Improve Agility, Minimise Time, and Optimise Manufacturing Quality
Raphael Morlec, ITS project leader, SANOFI
Christos Varsakelis, senior manager process modelling, GSK

ICSE: Outsourcing Formulation and Manufacturing

PHARMA INSIGHT BRIEFINGS
Location: ICSE Theatre—1G90

Tuesday, 9 October 2018, 11:50–12:20
The Vast Opportunities in the Emerging Markets for OTC and Pharma Players
Reiner Christensen, CEO, Chameleon Pharma

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

Tuesday, 9 October 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, Africa and Asia, Fresenius Kabi

Tuesday, 9 October 2018, 15:10–15:40
Technology Selection Methodologies for Addressing Bioavailability Challenges
Caroline Bauer, pharmaceutical development manager, Lonza Ploermel

Tuesday, 9 October 2018, 15:50–16:20
Recipharm Pathway to Clinic–From Formulation to Clinical Trial
Mikael Bisra, development and technology sales director, Recipharm

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

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

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

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

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

Innopack/P-MEC: Packaging and Manufacturing

KEYNOTE SESSIONS
Innopack/P-MEC Theatre—4F121

Tuesday, 9 October 2018, 10:30–11:00
Latest Consumer Trends in Packaging: Pharma Perspective

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MATEJ KASTELIC/SHUTTERSTOCK.COM

Chakravarthi AVPS, Global Ambassador, World Packaging Organisation

Tuesday, 9 October 2018, 11:10–11:40
A Personal Approach to Pharma Packaging: Shifting from Large Volumes to Personalised Solutions
Christopher Waterhouse, managing director, IDIPAC

Wednesday, 10 October 2018, 10:30–11:00
Pharmaceutical Packaging Innovations: Collaboration from Fundamental Science to Industrialisation
Clive Badman, head PTS pre-competitive activities, GSK

Wednesday, 10 October 2018, 11:10–11:40
New Strategies for Excellence in API Stability and Packaging Transportation
Speaker to be announced

Thursday, 11 October 2018, 10:30–11:0
Workshop: The Future of Sustainability in Pharmaceutical Packaging
Victor Bell, president, EPI - Global Environmental Packaging & Product Stewardship Consultants

Innopack/P-MEC: Packaging and Manufacturing

PHARMA INSIGHT BRIEFINGS
Innopack/P-MEC Theatre—4F121

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

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

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

Tuesday, 9 October 2018, 14:30–15:00
Ompi Nexa: The Glass Prefillable Syringe Choice for Biodrug Challenges
Martina Largoni, OMPI Pharmaceutical Systems EZ-Fill, OMPI

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

Tuesday, 9 October 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.

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

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

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

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

Wednesday, 10 October 2018, 16:30–17:00
Gx RTF ClearJect - a COP Syringe Made in Germany
Bernd Zeiss, manager technical support medical systems, Gerresheimer

Awards Celebrate Pharma Innovation

CPhI Pharma Awards recognize the achievements of experts who have developed innovative technologies, processes, and services to deliver effective drug therapies to patients around the world.

Now in its 15th year, the CPhI Pharma Awards recognize top innovator companies from the global bio/pharma community that have developed new approaches, technologies, and strategies to advance bio/pharmaceutical development, manufacturing, and industry efforts to promote patient well-being.

Winners in 17 categories will be recognized at a Gala Awards Ceremony on 9 October 2018 during CPhI Worldwide in Madrid, Spain. The ceremony will be held at the Grand Barcelona Ballroom of the Eurostars Madrid Tower Hotel.

The awards ceremony—an opportunity to celebrate the success of teams nominated for the awards—includes a three-course meal, wines, champagne, and entertainment. Participants can connect with more than 500 industry leaders in a celebratory setting, network, receive recognition, and boost their company's profile.

Awards are offered in the following categories:

Excellence in Pharma: API Development

Excellence in Pharma: Formulation

Excellence in Pharma: Excipients

Excellence in Pharma: Manufacturing Technology and Equipment

Excellence in Pharma: Bioprocessing & Manufacturing

Excellence in Pharma: Analysis, Testing, and Quality Control

Excellence in Pharma: Regulatory Procedures and Compliance

Excellence in Pharma: Drug Delivery Devices

Excellence in Pharma: Packaging

Excellence in Pharma: Supply Chain, Logistics, and Distribution

Excellence in Pharma: Contract Services and Outsourcing

2018 CPhI Pharma Awards Gala

9 October 2018
Grand Barcelona Ballroom
Eurostars Madrid Tower Hotel, Madrid, Spain
For information: awards.cphi.com/gala

2018 CPhI Pharma Awards Recognize Excellence in Pharma

Excellence in Pharma: Regulatory Procedures and Compliance

Excellence in Pharma: Corporate Social Responsibility

Excellence in Pharma: CEO of the Year

Excellence in Pharma: Pharma Company of the Year

Excellence in Pharma: OTC

Excellence in Pharma: Patient Centricity

Excellence in Pharma: IT, mHealth & Digitilisation

Tickets for the gala are available for tables and individual seats. For more information, visit awards.cphi.com/gala

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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

9 October 2018: 9:30–17:30
10 October 2018: 9:30–17:30
11 October 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 9 September 2018.

A fee of €50 is charged from 10–23 September 2018.

A fee €140 is applicable on or after 24 September 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 entrace to the CPhI Pharma Awards Gala. Visit https://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.

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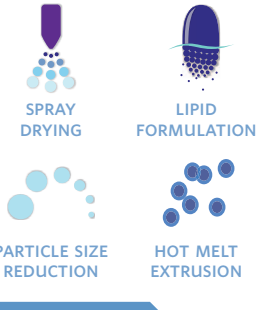

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