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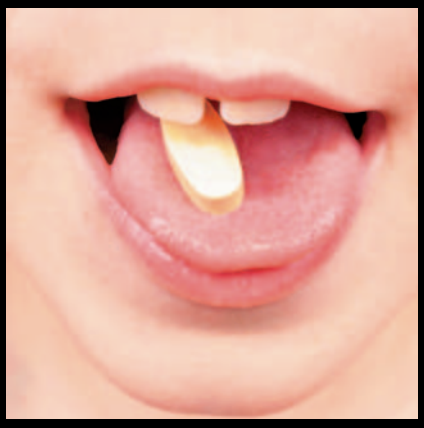


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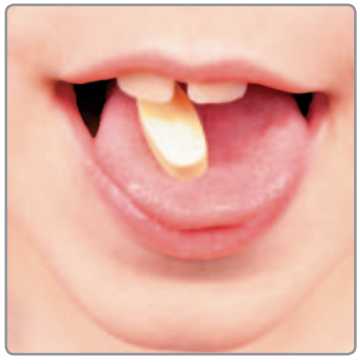
Removing the Bitter Taste from Drug Development

Peter Scholes



BORIS SOSNOVYY/SHUTTERSTOCK.COM

Integration of formulation development, real-time adaptive GMP manufacturing, and clinical testing using a consumer preference panel can save time and cost in performing taste-masking assessments.

The development of effectively formulated oral drug products is key to ensuring patient compliance and desired clinical outcomes. Given the increasing regulatory expectations for the development of bespoke age-appropriate products, critical performance features now include palatability and overall acceptability in addition to standard drug-delivery requirements for oral medications. Understanding and modifying the taste attributes of aversive drug substances is, therefore, important. There are several taste-masking techniques available, which involve either modification of the API itself or the formulation; however, there are as yet no standardized industry approaches for assessing whether the poor taste of a drug has been effectively masked. Although *in-vitro* and preclinical methods can be applied, the resulting data are, at best, incomplete and, at worst, misleading. Approaches that have greater correlation with human response and, ideally, incorporate clinical assessment of the formulation are, therefore, required. This article reviews the breadth of taste-masking techniques available, the methods used to evaluate taste, and how an integrated approach to formulation development and clinical assessment can deliver significant benefits for product development and validation.

Compliance and the need for taste masking

The growing industry interest in palatability and acceptability of medicines is driven primarily by issues around patient adherence and compliance. Compliance is a particular issue with pediatric and geriatric patients (1), with certain medicines only achieving 11% compliance in children (2). These populations are not only the most sensitive to taste, but are also the patient groups who suffer most from dysphagia or have difficulty in coordinating swallowing, making the need to generate age-appropriate medicines imperative.

Regulators are now stipulating the requirement for pediatric investigation plans (PIPs) and pediatric study plans (PSPs) for all new registered products, making compliance essential to development. Demand is also growing at unprecedented rates amongst the ageing population. The World Health Organization estimates that the number of people aged 60 years or over

Peter Scholes is chief scientific officer at Quotient Sciences.

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Table I: Summary of methods used to assess taste.

Technique	Method(s)
Modeling/*in-silico* tools	*In-silico* bitterness databases (e.g., BitterDB) are used to predict the taste characteristics of drugs in development (5).
Animal models	Rodent brief-access taste aversion (BATA) model, where the rodents' lick patterns and frequencies are used to determine the palatability of a molecule. Frog taste-nerve response, where the nerve is connected to an AC amplifier and responses to a bitter drug, in varying formulations, are recorded. The peak height obtained is used to assess taste masking.
Analytical tools	*In-vitro* methods, such as ultraviolet (UV) spectrophotometry, involve suspending the taste-masked formulation in water and analyzing the API concentration. If the free API concentration is below a certain threshold, then the formulation is deemed to have sufficiently masked the taste of the API. Electronic or e-tongue sensors can be used to mimic human taste perception across the five major taste categories (bitter, salty, sour, sweet, and umami). During the assessment, the formulation or API is evaluated against a reference material (e.g., quinine hydrochloride as a bitter model compound). The taste patterns generated are then used to determine palatability.
Human taste panels	Groups of healthy volunteers are asked to taste a potentially aversive drug, and provide qualitative or quantitative information on several defined attributes to characterize taste and palatability parameters. Formulations are then developed with the aim of overcoming these challenges before a second assessment in human subjects to confirm acceptability. Selected formulation(s) can then progress (back) into clinical trials.

is predicted to grow to 1.4 billion by 2030, and nearly 2.1 billion by 2050—more than double the number in 2015 (3). The so-called "silver tsunami" is poised to become one of the most meaningful social transformations of the 21st century.

Current approaches to masking taste

The palatability of a medicine is largely dictated by the taste of the API. A significant percentage of APIs on the market or in development are bitter tasting or unpalatable. In most cases, taste issues can be overcome by simply formulating the API into a tablet or capsule. This approach, however, cannot be used as standard in pediatric and geriatric populations because of swallowing difficulties associated with oral administration. Here, alternative formats such as liquids, suspensions, or dispersible or chewable products must be used.

A number of physiological and physicochemical approaches have been employed in an attempt to mask the taste of APIs and/or to prevent drugs from interacting with taste buds. These approaches fall into four main categories, outlined below and discussed in more detail in the paper published by J. Walsh *et al.* in 2014 (4).

API modification. API modification involves generating a new solid form or salt of the API, or administrating it as a prodrug. These approaches, however, are not always viable as the API may have just one stable form, or it may not be possible to form a salt with the neutral API.

Flavorings/excipients. Components such as sweeteners, flavorings, or solubility modifiers can be added to the formulation to overcome the taste of the API. This method is generally problematic for high dose APIs, where it may not be possible to mask the taste.

API complexation. The API can be complexed with a number of ligands to prevent the molecule interacting with taste receptors. These ligands include cyclodextrins, ion exchange resins, and polymers. This method is only possible with relatively low drug loading. The potential risk of altering the pharmacokinetic (PK) performance should also be considered.

Coatings on tablets/capsules. Coatings can be used to effectively cover the drug product and prevent the API from being released in the mouth. Coated formats, however, do not overcome issues with swallowing and lack of compliance. In addition, coatings add significant cost to the production process and may also affect the release and PK profile of the drug.

Beyond palatability and API properties, it is also necessary to consider broader drug-delivery needs when designing a taste-masked formulation. Factors such as requirement for solubilization enhancement; excipient stability limitations; patient age (and therefore the acceptable daily intake of excipients); whether the API must be taken with water or food; and impact on storage requirements (i.e., the need for refrigeration), all make the design of taste-masked formulations more complex, and the effective assessment of taste more important.

Methods used to assess taste

There is no standard industry approach defined for assessing and verifying whether a drug product's taste is acceptable. Although there is a range of commonly used techniques, outlined in **Table I**, the lack of standardization presents a significant issue in determining the taste of drug products.

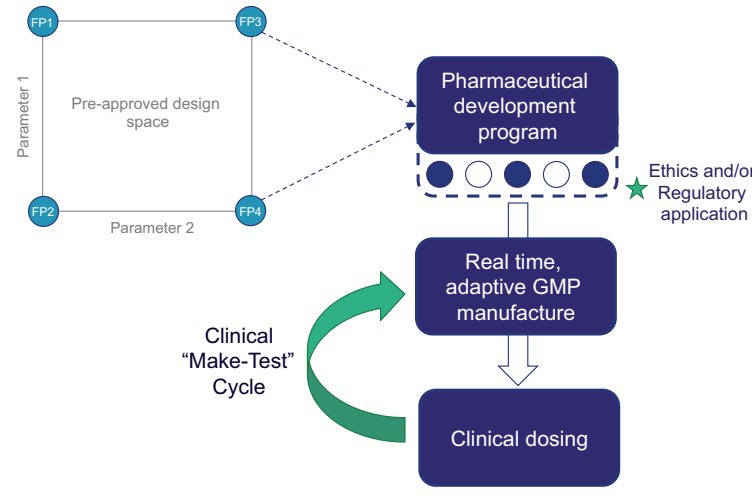
All of the techniques, apart from human taste panels, are problematic in that they are surrogate methods, and, therefore, do not necessarily predict or match the human response. There is also additional time and cost associated with formulating and

Table II: Example consumer preference panel questionnaire.

Attribute	Strongly dislike	Dislike	Slightly dislike	Neither like nor dislike	Slightly like	Like	Strongly like
Smell							
Sweetness							
Bitterness							
Mouthfeel							
Texture							
Grittiness							
Difficulty to swallow							
Aftertaste							
Overall acceptability							

performing these surrogate analytical or preclinical tests. If the formulation is subsequently deemed unsuitable from a taste perspective in humans, further development cycles may be required, adding yet more cost and time to the process. It is, therefore, imperative that formulation selection is based on clinical taste assessments. Limitations can still be apparent if an acceptable formulation is not identified from the initial raft of prototypes prepared for human testing, highlighting a preferred need for a test model that allows flexibility to make compositional adjustments in real-time based on arising sensory data.

Figure 1: Quotient Sciences' integrated "make-test" cycle using a pre-approved, flexible formulation design space.



Rapid development and assessment of taste-masked products

The integration of formulation development, real-time adaptive GMP manufacturing, and clinical testing has been successfully used for both the assessment of taste and sensory attributes of drug substances, as well as the rapid screening of prototype taste-masked formulations. This model reduces development time and cost (given drug products are prepared within hours or days of dosing), and maximizes the potential for success, given adjustments to compositions are based on arising human clinical data (e.g., safety, tolerability, PK, pharmacodynamics [PD], or taste). As shown in **Figure 1**, flexibility can be enhanced by up-front definition of a formulation design space with bracketing ranges in the levels of critical-to-performance excipients.

To perform the taste assessments, a consumer preference panel is established, typically of 12–18 subjects, using healthy adult volunteers trained in "sip and spit" tasting techniques. The emphasis of the panel is on "preference" rather than "measuring levels" of taste, providing representative data on acceptability of a formulation to a general population. Participants complete a bespoke questionnaire, consisting of visual analogue or hedonic scales to characterize a variety of API and formulation parameters, an example of which is shown in **Table II**. The scale will typically give seven ranking levels, ranging from "strongly like" to "strongly dislike." Several formulations can be assessed within a single day, with a one- to two-hour gap between tasting events.

The program design and taste-assessment protocol are customized to the specific API and formulation in question. Design space variables can be established for API properties (e.g., particle size) or formulation attributes (e.g., levels of sweeteners, flavors, or viscosity modifiers). The protocol can also include assessments of API only (at single or multiple concentrations), positive controls (e.g., quinine for bitterness), the inclusion of replicate assessments to serve as further controls, and/or the use of multiple study periods to allow for interim analysis of data to guide decision making.

Performing these studies within the United Kingdom

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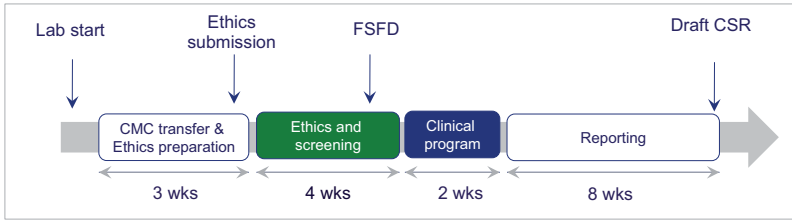
Figure 2: Summary of the development and clinical program for taste-masked formulations of RDX7675. CMC is chemistry, manufacturing and control. CSR is clinical study report. FSFD is first subject, first dose.



requires submission to and approval from an Independent Ethics Committee (IEC). Whether a regulatory review by the Medicines and Healthcare products Regulatory Agency (MHRA) is required will depend on study objectives, specifically if safety assessments are required.

Combining taste and pharmacokinetic evaluation

While taste assessments can be used as the sole clinical endpoint, they can also be combined with PK measurements as part of the same study. This approach can be particularly important if the taste-masking strategy has the potential to affect the PK performance of the existing (adult) formulation. The drug half-life requires a washout period, meaning that a taste evaluation can be incorporated into the study design without delaying the product assessment cycle (which is typically one to two weeks). The result is a powerful combination of clinical data confirming product palatability and acceptability, coupled with a full understanding of the PK performance in humans. In combination, this presents an ability to transition to efficacy studies in the target patient population with confidence, with an appropriate formulation, and with an informed dosage regimen.

The following case study demonstrates how the Quotient Sciences approach facilitated the rapid redevelopment of a taste-masked formulation for the long-term treatment of hyperkalemia (6).

Development and assessment of taste-masked formats for chronic disease

Background. Patients with heart failure or chronic kidney disease are at high risk of developing the potentially life-threatening condition hyperkalemia. The current approved treatment, sodium polystyrene sulfonate, has poor palatability and is unsuitable for long-term use. RDX7675 is a novel product being developed for the treatment of hyperkalemia. RDX7675 is a structural derivative of sodium polystyrene sulfonate and, therefore, shares some issues with taste and palatability. The goal was to expedite development of a clinically validated formulation for RDX7675, which suitably masked its taste, to enable its long-term use in the treatment of hyperkalemia (6).

Approach. Rapid screening of multiple formulation types and flavors was undertaken. All formats were manufactured within 24 hours of dosing requirements. A flexible clinical protocol ensured that any required changes to the formulation, flavor, or viscosity could be made within the study. A total of 18 subjects were included on the consumer preference panel in the two-period clinical study. Formulations were tasted every two hours, with doses expectorated, and palettes cleansed with water and unsalted crackers between tastings. Data were captured via questionnaires.

Output and impact. The flexible study design enabled real-time manufacturing and rapid taste assessments of multiple formulation options. Data from the consumer preference panel were available within nine weeks of program initiation. These data enabled the selection of a lead formulation to progress to the pivotal PK/PD clinical study (**Figure 2**).

Conclusion

The need for taste-masked products continues to grow as a result of the significant number of unpalatable drugs in development and the requirement for age-appropriate delivery formats. The *in-vitro* and preclinical methods used to assess whether a formulation has effectively masked the taste of an API show poor correlation with human response, particularly where pediatric medicines are concerned (7). Where sensory human taste panels are used to quantify specific criteria with great precision, highly trained subjects are required, with the associated additional costs and timelines.

By integrating formulation development, real-time adaptive GMP manufacturing, and clinical assessments using consumer preference panels, formulations can be rapidly screened and their taste characteristics assessed. Acceptable taste-masked formats can be identified and optimized in real-time based upon arising sensory and/or PK data. Generated data can be used both to inform further development, as well as support compilation of PIPs and PSPs.

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Transition From Clinical to Commercial Supply Chain—Regulatory Starting Materials

Valdas Jurkauskas and Minzhang Chen

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The authors discuss expectations of regulators on the selection of drug substance regulatory starting materials (RSM) and the justification of their designation in the pharmaceutical supply chain, the scope of the RSMs' presentation required in regulatory filings, and how to mitigate and prepare for "push backs" in the event of a major objection to the sponsor's RSM designation.

Valdas Jurkauskas, PhD, is vice-president and head of Chemistry, Manufacturing and Controls (CMC) at Akebia Therapeutics and **Minzhang Chen, PhD**, is CEO of STA Pharmaceutical, a WuXi AppTec company.

Pharmaceutical businesses are rapidly becoming global, with approximately half of the industry's growth in emerging markets (1). A pharmaceutical company's objective is, therefore, to build a sustainable and cost-efficient supply chain that meets global regulatory requirements. The selection of drug substance regulatory starting materials (RSMs) and justification of their designation in the pharmaceutical supply chain has become an industry-wide focus as a measure of mitigating regulatory risks and preventing unexpected rises in cost when transitioning from clinical to commercial supply chain. This article discusses the expectations of regulatory agencies, the scope of the starting materials' presentation in the filings, and the risk and readiness for a "push back" (i.e., extension of the GMP portion of the API process upstream) in the event of an agency's major objection to the sponsor's RSM designation.

Pharmaceutical supply chain

The pharmaceutical supply chain can be divided into four segments, as shown in **Figure 1**, from starting materials (i.e., the RSM), to the drug substance, the formulated drug, and ultimately, the packaged and labeled finished product.

Commonly, the emphasis during pharmaceutical development is on the portion downstream of the RSMs. The part of the supply chain upstream of the starting materials does not receive the same level of attention—less time is allocated for development of process and specifications, which can, therefore, present a regulatory risk and potential for an unexpected rise in cost when transitioning from clinical to commercial supply chain. One particular risk factor is the development of RSMs, or the lack thereof.

Typically, at the time of marketing application submission, the sponsor would have validated the production processes of the drug substance, formulated drug, and finished product. This validation involves successfully conducting at least three consecutive commercial-scale batches for each segment of the supply chain and releasing each batch against pre-defined acceptance criteria (i.e., commercial specifications). If, at this advanced stage of development, the proposed RSM

designation is not accepted by a regulatory agency, then the entire supply chain that stems from this RSM is essentially invalidated. The sponsor will likely experience lengthy delays to address RSM designation issues before the marketing application is approved.

RSM designation

One of the most underrated risks is for sponsors to assume that RSM designations used throughout clinical trial applications will be accepted in the marketing application without justification. An industry-wide disagreement on terminology—resulting in a plethora of names related to starting materials, such as raw materials, key raws, critical raw materials, key raw materials, critical raws—further confuses the role of starting materials in the supply chain. To clarify, an API RSM could be a raw material, a manufacturing process intermediate, or even an API. The material could be an article of commerce that is available from multiple sources, typically in large quantities and often sourced under commercial agreement. The material could be produced in-house and manufactured using custom-designed process. The RSM should be used in the production of API and it should represent a significant structural fragment of the API's chemical structure. The sponsor of the clinical or marketing application should designate the RSMs and document rationale for their selection (2). The RSM's designation marks the point at which GMP production (described in Section 3.2.S.2.2 of CMC module 3) (3) of the API begins, as shown in **Figure 2**.

EMA reflection paper

In 2014, the European Medicines Agency (EMA) published a reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances (4). EMA felt that the current guidelines lacked detailed specifics, thus leading to a variety of interpretations. Proposed starting materials specifications were often insufficient. EMA even encountered instances where starting materials were not discussed in the application or processes by which the starting materials prepared were not part of the overall criticality appraisal. More recently, the International Council for Harmonization (ICH) Q11 guidelines implementation group published two documents of questions and answers to clarify the ambiguity and provide additional examples for the selection and justification of starting materials (5). These documents are extensions of the original Q11 guidelines (6).

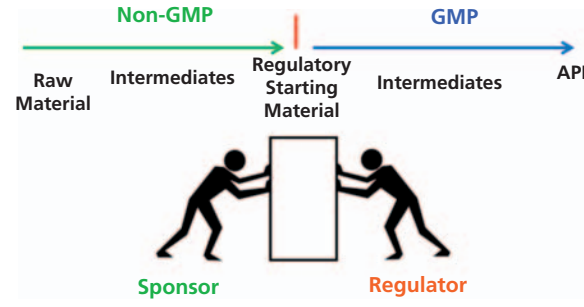
As a guidance to industry, EMA included seven examples of critical manufacturing steps that should be performed under GMP:

- Steps involving the formation and/or purge of key impurities
- Steps that introduce key structural features of the active substance
- Steps requiring careful control of process parameters
- Steps that use or generate genotoxic compounds
- Steps that involve the use of class 1 solvents and/or toxic metals
- Complex chemical transformations
- The final purification step.

While the last example in this list pertains to the final isolation and purification step of drug substance, which should be performed under GMP setting, the first six examples are quite broad and could apply to the non-GMP portion of the drug substance process where RSMs are produced. For instance,

Figure 1: Schematic presentation of four segments of the pharmaceutical supply chain.

Figure 2: Schematic presentation of API-only supply chain segments.



FOUR COMPONENTS TO ACHIEVE READINESS TO TRANSITION FROM CLINICAL TO COMMERCIAL SUPPLY CHAIN

- Locking the manufacturing processes for drug substance and drug product as well as having evidence of adequate stability for each segment of the supply chain (12-month stability data are expected, according to International Council for Harmonization Q11 guidelines)
- Determination of critical quality attributes (CQAs) for the API and formulated drug
- Agreement with regulatory agencies worldwide on the regulatory starting material (RSM) designation
- Assessment of manufacturing process parameters, establishment of their acceptable operating ranges, and determination of critical process parameters (CPPs) and the variability range that would affect the CQAs of the API or formulated drug

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Figure 3: API-only supply chain and reasons for starting material designation rejection.

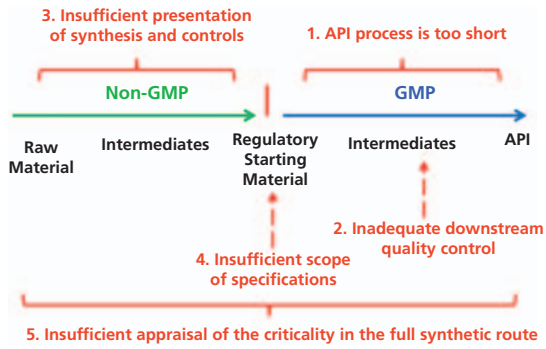


Figure 4: Schematic presentation of original API GMP process.

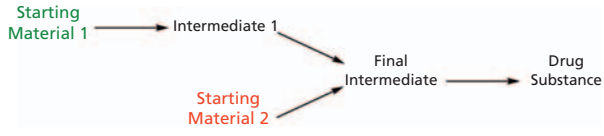
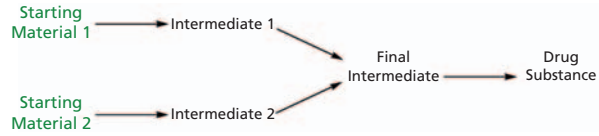


Figure 5: Schematic presentation of updated API GMP process.



"careful control of parameters" is expected in any manufacturing process. Furthermore, the definition of "complex chemical transformation" is somewhat subjective because any chemical reaction will have its own intricacies. Thus, the probability of EMA's push back of a proposed RSM designation is quite high.

Reasons for rejection of RSM designations

Figure 3 shows the API portion of the supply chain and frequently encountered reasons for regulatory agencies to reject proposed RSM designations. It is important to note that the whole supply chain is impacted.

The most common reason for rejection of a RSM designation is the insufficient number of steps (#1 in **Figure 3**)in the API manufacturing process (CMC Section 3.2.S.2.2) (3). Lack of in-process controls or inadequate acceptance criteria for formally released GMP intermediates (CMC Section 3.2.S.2.4) (3) represent inadequate quality control and is another common reason (#2 in **Figure 3**) for the rejection of a RSM designation.

The insufficient presentation of synthesis and controls for RSMs (CMC Section 3.2.S.2.3) (3) could also be the reason (#3 in **Figure 3**) for rejection of a RSM designation. Regulatory agencies expect API-like acceptance criteria for RSMs, thus insufficient scope of specifications is another reason (#4 in **Figure 3**) for major objection to a RSM designation. Lastly, the reviewer may determine that there was insufficient appraisal of criticality in the full synthetic route (i.e., from raw material or building block to API), leading to rejection of the RSM designation (#5 in **Figure 3**) (7, 8).

Readiness for push back

Successful defense of RSM designation is not guaranteed; therefore, the sponsor should preemptively work on three areas to prepare for possible push back: chemical synthesis, analytical controls, and manufacturing.

Chemical synthesis plays an important role because the extent of push back will depend on the synthetic route. As part of the synthetic route scouting strategy early on in process development, the sponsor should identify an earlier intermediate as a back-up RSM. The push back will result in an increased number of GMP steps upstream, requiring in-process analytical controls and adequate scope of acceptance criteria for the back-up RSM.

The rejection of RSM designation can lead to two scenarios. If the RSM was produced at a non-GMP plant, the sponsor would have to transfer production to a GMP plant, which can be stressful, especially if the sponsor learns about the major objection to the RSM designation in a pre-new drug application meeting or during marketing application review. The sponsor would be in a more favorable situation if the rejected RSM was produced at a GMP plant. They would then have an opportunity to retroactively validate RSM process at the same manufacturing site, in the same equipment, and on the same scale, and retain all commercial inventory, including all drug substance and formulated drug batches already derived from this RSM.

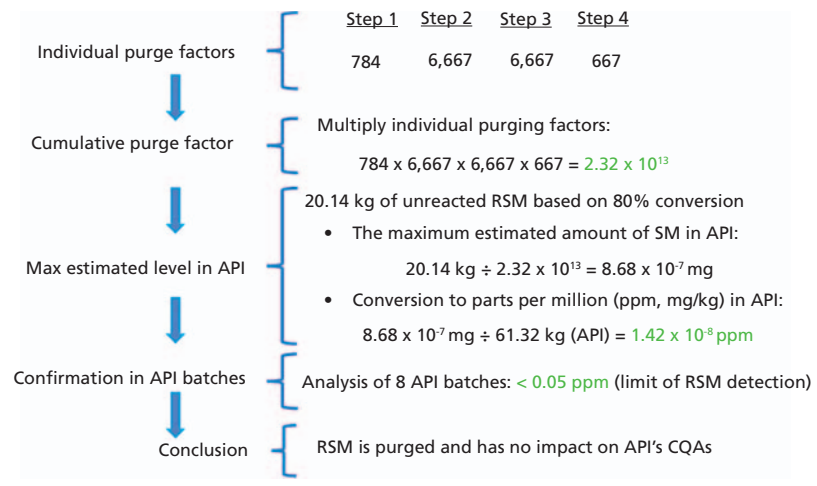
Case study: addressing FDA's push back and retaining launch inventory

The following case study is presented to illustrate use of a back-up RSM. A schematic presentation of validated commercial process for the preparation of API is shown in **Figure 4**.

The proposed RSMs 1 and 2 were produced using a custom designed manufacturing process (i.e., neither of the RSMs was an article of commerce). RSMs 1 and 2 constituted 38% and 31% of the API's core atoms, respectively. The core atoms are defined as all API structure atoms in the required connectivity and spatial orientation, excluding hydrogen atoms. Hence, RSMs 1 and 2 could be viewed as custom designed building blocks of similar complexity. Yet because RSM 1 was an additional step "away" from the API formation, the two RSMs had different propinquity to the API (see **Figure 4**). As a result, the API GMP process lacked symmetry in its synthetic hierarchy.

FDA accepted the proposed RSM 1 designation, but rejected the proposed RSM 2 designation, stating that the latter is used in the API making step, and thus is considered an advanced process intermediate and should be produced under GMP. The sponsor had anticipated a push back and had identified a precursor to RSM 2 as a potential starting material. As a risk mitigation measure, the sponsor developed appropriate GMP-level analytical controls and acceptance criteria as back-up preparation for RSM 2. Furthermore, the sponsor had produced all RSM 2 batches in a GMP plant, creating an opportunity to retroactively validate RSM 2 process in the same equipment, on the same scale, and at the same manufacturing site, hence, enabling retention of all downstream commercial launch inventory originating from RSM 2 to the API and formulated drug to the finished packaged and labeled product.

Figure 6: Example of a regulatory starting material (RSM) fate analysis in the API process. CQA is critical quality attribute.



In the updated API process, RSMs 1 and 2 constituted 38% and 20% of API's core atoms, respectively, and could be viewed to have similar complexity, custom-designed building blocks with identical propinquity to the API (see **Figure 5**). As a result, the API GMP process had symmetrical synthetic hierarchy.

Using CQAs to address push back

In another scenario, there is a possibility that FDA could accept the proposed RSM designation, while EMA rejects that same designation. The sponsor could accept the major objection to the RSM designation and extend the GMP portion of the API process upstream. In this scenario, the sponsor would be forced into a complex, two-stream supply chain, one for the US market and another for the EU market. Alternatively, the sponsor could overcome objection by presenting a comprehensive assessment of the RSM's impact on the CQAs of either API or formulated drug.

CQAs are justified by an impurities assessment. There are two types of impurities:

1. Those structurally related to the API, such as starting materials, process intermediates, and their by-products.
2. Those structurally unrelated to the API, such as reagents, solvents, and their by-products.

A laboratory-based R&D study, where high levels of process materials and impurities are purposefully introduced in the process (i.e., "spiking"), can assess an impurity's fate by measuring their residual levels after one or more operations. Data from such studies can be used to calculate the estimated maximum level of any material in the API. Laboratory results are typically confirmed by analyzing manufactured batches of the API and corresponding process intermediates.

The fate analysis of a RSM in the process and assessment of its impact to the API's CQAs is presented in the example in **Figure 6**.

The API manufacturing process consisted of four distinct manufacturing steps. A high quantity of RSM was spiked in each step and the amount that remained upon completion of the step was measured. Individual purging factors (see **Figure 6**) were calculated by dividing spiked quantities with the amount that remained. Iterative multiplication of all individual factors yielded a cumulative purging factor of 2.32 x 10^{13}. To help reviewers appreciate how effectively the RSM is purged in the process, the maximum estimated level for this material in the API was calculated. The actual kilogram quantities of the RSM (100 kg) input and corresponding API (61.32 kg) output were used. A conservative assumption was made that only approximately 80% of the RSM will convert to the API, leaving approximately 20% of unreacted material, corresponding to 20.14 kg. Division of this residual amount by the cumulative purging factor (2.32 x 10^{13}) yielded the maximum estimated level, 8.68 x 10^{-7} mg, in the API. This quantity was converted to a more common presentation of concentration for an ultra-low-level impurity: parts per million (ppm = mg/kg). Division of the maximum estimated level (8.68 x 10^{-7} mg) by the API batch output (61.32 kg) yielded 1.42 x 10^{-8} ppm.

The purging study findings were confirmed by analysis of eight API batches with a method that could detect residual RSM at a level as low as 0.05 ppm. In summary, the results from analysis of laboratory-scale purging studies and manufactured batches conclusively demonstrated that the proposed RSM was purged in the process and had no impact on the API's CQAs. The study results enabled the sponsor to exclude the analysis for this RSM in the API acceptance criteria. Agencies worldwide accepted the justification for this RSM.

Contin. on page s22

A QbD Approach to Shorten Tablet Development Time

Regis Cazes

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Reducing "time to market" is the ultimate goal for every pharmaceutical lab. Being the first on the market brings a competitive advantage for prescription, over-the-counter, or generic-drug manufacturers. Applying quality-by-design (QbD) principles at the formulation phase can prevent tablet defects at an early stage and thereby drastically reduce time during the complex and troublesome phase of "scale-up." Waiting until late in development in the "production-size phase" may force scientists to solve formulation issues at the pilot level or—even worse—in actual production. A QbD approach, however, secures the scale-up to production with maximum safety right from the beginning.

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Tableting instruments (i.e., compaction simulators) that simulate high-speed presses can be used in a quality-by-design (QbD) approach to perform in-depth material characterization and direct scale-up. Because they can modify the strain rate (i.e., the linear vertical punch velocity), tableting instruments can mimic the dynamics of a rotary tablet press running at full speed. The determination of the right material and quality attributes (e.g., lubrication, elasticity, cohesiveness, weight variation) can help in developing a robust formulation. An extensive characterization of a formulated blend can also prevent capping, sticking, or even die binding on a commercial-size rotary tablet press.

Preventing lamination or capping

Lamination and capping are common tablet defects occurring in tablet manufacturing. Both terms are used to describe cracks on the side of the tablet. Lamination is a defect exhibiting cracks on the cylindrical part of the tablets (i.e., the "belly band") as shown in **Figure 1**. Capping is a defect occurring at the junction between the cylindrical part and the convex part of the tablet (see **Figure 2**). Even though lamination and capping look more or less the same, some of their causes can be different.

Lamination. Lamination is due to air entrapment, as shown in work from the University of Bordeaux (1). An entrapped bubble of air begins to appear on the tablet surface at a pressure just below the pressure where lamination (cracks) can be observed. Applying pre-compression is then a efficient remedy. This de-aeration step will help remove the excess air. The ratio of pre-compression and main-compression can be studied. A pre-compression ratio of 10–30% is typically used in commercial-scale manufacturing.

This air-entrapment can also come from a tight clearance of the compression tooling. Every manufacturer has its own mechanical tolerance between the punch tip and the die bore. However, a very tight tolerance is not recommended as the air will have a hard time escaping from the powder bed and will thus create air bubbles. Reversely, too large of a tolerance creates powder loss mainly on the lower punch.

A tableting instrument can be used to troubleshoot or predict lamination issues. In a study performed with one of

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Figure 1: Lamination, a defect exhibiting cracks on the cylindrical part of the tablet (the "belly band").

Figure 2: Capping, a defect occurring at the junction between the cylindrical part and the convex part of the tablet.

Medelpharm's clients, a blend was compacted on a high-speed single punch tableting instrument using compression tooling from two different suppliers. Mimicking a Kikusui rotary tablet press at high speed, the tablets made with the first punch set had no lamination. The tablets made with the second punch set revealed lamination, although all the process parameters were identical with both punch sets. The cause of lamination was attributed to the difference of mechanical tolerances between the punch tip and the die bore. In this case, the tableting instrument was used to troubleshoot manufacturing issues and pin-point the parameter to be adjusted (i.e., change punch supplier).

The effect of mechanical tolerances at the formulation phase is something formulation scientists could take into account. This example demonstrates that such process parameters should be considered in the first steps of QbD.

Capping. Capping has its origin in the chemical nature of the excipients and APIs, the tablet shape, and process parameters, such as the turret speed, compression/edge thickness (and the resulting compression force), or insertion depth (i.e., penetration depth). Capping is ingloriously famous because it generally occurs during scale-up, either at the clinical manufacturing stage or during scale-up on a commercial-size rotary press. If tablet capping is discovered at a late stage, reformulation is most likely not an option anymore.

The first process parameter that can be adjusted is the convexity of the tablet by modifying the radius of the punch tip to reduce capping tendency. Computer simulation (2) using finite element modeling has shown that a radial (i.e., shear) stress appears on the tablet cap when the upper punch tip is moving away from the tablet surface. The upper punch first loses contact at the land (i.e., the little flat portion surrounding the punch tip), which creates stress in the radial direction, explaining why capping occurs in the land region. Some experienced tableting experts know that the higher the curvature (i.e., the lower the radius), the higher the risk of capping tendency. Thus curvature becomes another process parameter to be evaluated in a QbD approach.

The effect of mechanical tolerances at the formulation phase is something formulation scientists could take into account.

"Flattening" the tablet has its limits, however, especially when the tablets have to be film coated. Trying to coat flat-face tablets generally result in a defect known as "tablet twinning," where two tablets are glued together.

The second process parameter that can be adjusted after the tooling shape is the pre-compression. This will remove excessive air inside the powder bed and most likely enhance the cohesion of the tablets. This additional cohesion should most likely counterbalance the shear stress inherent to the tablet shape and avoid capping.

The third process parameter is the insertion depth, also called upper punch penetration. By compacting deeper into the die, the applied pressure becomes symmetrical, thus densifying and creating cohesion equally on both sides of the tablet. Similar to adjusting pre-compression, the additional cohesion on the upper part of the tablet might be enough to prevent capping.

A fourth process parameter is the compression/edge thickness (i.e., distance between the punch). By increasing the compression thickness, the compression force will be mechanically decreased and capping should disappear rapidly. The tablet breaking force (cohesion) will also drop, however, and it will most likely change the disintegration time and dissolution profiles as well. This process parameter needs to be assessed carefully.

Adjusting all these parameters using a commercial-size press is time-consuming and requires large quantities of blend, but it is possible to evaluate capping by using single

FIGURES ARE COURTESY OF THE AUTHOR

punch presses with high strain rate capabilities. The experiments described previously can be performed on such compaction simulators to troubleshoot tablet defects with small quantities of blend in a timely manner.

The process parameters studied to troubleshoot the defects can be evaluated during formulation to determine the process space to produce good tablets without capping or lamination.

QbD for tablet formulation

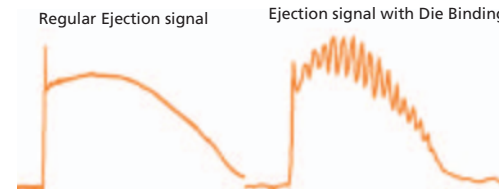
Formulators can use QbD to optimize a formulation in the early development stage, before scaleup. Based on the quality target product profiles (QTPP) and the process flow chart (wet/dry granulation, tableting, coating), formulation scientists will have to list the material attributes (MA), quality attributes (QA), and process parameters (PP) that are required to achieve the QTTP. This risk assessment, based on the scientist's process understanding and experience, shall then pinpoint the critical attributes and parameters and assess them with the compaction simulator.

As described earlier on capping and lamination, the process parameters studied to troubleshoot the defects can be evaluated during formulation to determine the process space to produce good tablets without capping or lamination.

Tabletability. Material attributes of the API and excipients generally include physico-chemical attributes, such as assay, impurities, particle size distribution, flow indexes, water content, and others. The compactibility of the ingredients, however, is not always taken into account for a simple reason: excipients have to comply with the monographs listed in the pharmacopeias, and these monographs do not contain any functionally-related specifications. Surprisingly, an excipient designed for direct compression does not have any specifications on its ability to form bonds, which is what should be expected from a binder. A scientist getting an *United States Pharmacopeia (USP)/European Pharmacopoeia (Ph. Eur.)* compendial excipient shall only rely on the supplier's brochure on its performance in tableting. This is the same for an API for which it could be possible to test its ability to form bonds under pressure.

A generic-drug manufacturer, for example, that intends to source an API from different drug substances suppliers should consider various properties. In addition to the chemical purity criteria and other common physical characteristics, such as particle size distribution or specific surface area, it is wise to make a tabletability profile on an instrumented tablet press. Due to the poor flowability of APIs and small quantity of available API at this stage, the loading of the die would most likely be carried out manually. (Note that external lubrication with a dry lubricant on the die bore and punches is often necessary to avoid sticking and die binding.) If the API is able to form bonds, it's then possible to plot the tensile strength vs. axial pressure, as defined by *USP* Chapter <1062>, which was introduced in June 2017 (3). This tabletability profile can be used to compare the different grades of API, and can help choosing the right grade for the drug product. This approach can be performed the same way on neat excipients.

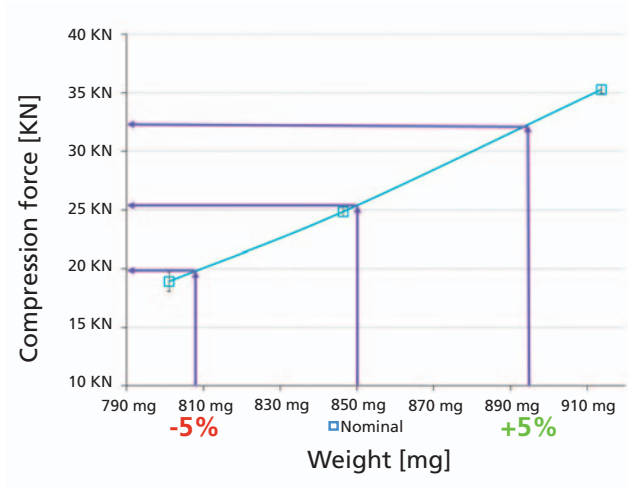
Figure 3: Ejection signals–Die binding vs. regular.



Lubricant. Evaluation of lubrication and the determination of criticality of certain material attributes should also be performed. It is widely thought that a quantity of 0.5–1% of lubricant is necessary in the tablet formulation. But is this correct? The obvious quality attribute to look at is the ejection force. However, there are other QAs that can be studied. First, the ejection force is only the peak of the complete ejection force signal. By taking a close look at the signal, it is possible to see oscillations on the signal just after the peak (see **Figure 3**). Even if the peak of the ejection force is still fairly low, this is a sign that die binding (also known as die tightness) is occurring. A less common approach is to consider also the transmission coefficient (4), defined as the ratio of the upper and lower punch force. To measure those forces, an R&D press will have to be equipped with force sensors on both punches and be able to operate the punch in a non-symmetrical way.

Older, common technologies, such as eccentric R&D presses, can do the trick if they are well instrumented. The compression force recorded by the lower punch will be systematically lower than the force recorded by the upper punch. The powder densification occurs first at the upper side of the powder bed. The energy provided to the system will be partially lost due to friction between particles and between particles and the die bore. This energy loss will result in a measurement of a lower punch force. The target of the transmission coefficient should be between 90% and 100%. A low transmission ratio, such as 70%, might be linked to ineffective lubrication. By looking at the peak of the ejection signal, the oscillations of the ejection signal, and the transmission ratio, the quantity of lubricant and its associated blending process

Figure 4: Force vs. weight variation.



can now be optimized. Different grades of magnesium stearate, a well known lubricant, featuring different specific surface areas, can give very different lubrication.

Elastic recovery. Elastic recovery is another parameter seldom assessed. Acquiring these data requires the tablet press to be instrumented with position sensors. The elastic recovery is the difference between the tablet thickness measured out-of-die, with a caliper for instance, and the in-die tablet thickness measured by the sensors at the peak of compression. Elastic recovery is often linked to lamination as it can create micro-fractures within the tablets. Interparticular cohesion is therefore reduced and lamination can occur. As an example, calcium phosphate excipient exhibits an elastic recovery around 4%. But some sustained release polymers can be as high as 20%. Generally speaking, it is recommended to associate ingredients having similar mechanical properties, especially when formulating bi-layer tablets where an elastic layer could induce a layer separation.

Compression force. The compression force is quite often considered as a process parameter. Actually, it is first a quality attribute. On a basic rotary tablet press, an operator can adjust the dosage height (and its corresponding quality attribute "tablet weight") and the compression/edge thickness. The compression force is then measured by strain gauges located on the pressure rolls. Decreasing the compression thickness will result in increasing the compression force and vice versa. That is the main reason why many people think that this compression thickness knob is controlling the compression force. Now, when the operator increases the dosage height, the compression force will also increase. In this case, compression force cannot be a process parameter and is in fact a quality attribute.

On the other hand, modern rotary tablet presses are equipped with a "weight control loop". This control loop will basically rely on the relation that exists between the tablet weight and the compression force. (One exception is GEA, formerly Courtoy, which uses the relation between tablet weight and tablet thickness.) The strain gauges measuring the compression force are the indicators to monitor the tablet weight. Any variation of the compression force will be an indication of a variation of tablet weight, most likely due to a non-uniform blend density and flowability between the beginning and end of the batch. A control loop will then electronically change the dosage height to maintain the compression force within the target value (i.e., set point). A production press is mechanically designed to compress the powder bed to a given volume, ensuring that similar force indicates similar weight. In this case, the particular set point for compression force is a process parameter. Depending on the context, compression force is both a QA and a PP.

Considering compression force as a QA can help a formulator speed up tablet development, by plotting the relation between the compression force and the tablet weight. To do that, the PP "dosage height" has to be modified to mimic a change in powder density during the process. For example, if the nominal tablet weight is 850 mg, the dosage height can be adjusted to reach 850 mg + 5% and 850 mg – 5%. Tablet weights within this range are compliant with the uniformity of mass test as set forth by the *Ph. Eur.* (5). The scientist can now plot the compression force versus tablet weights (see **Figure 4**). This graph will be crucial to help set up the ejection and tolerance set points on the commercial-size rotary tablet press during scale-up, thus saving time and material. In addition, other QAs, such a tablet breaking force (also known as "hardness"), disintegration time, or even some key dissolution times can be plotted versus tablet weight. All these graphs will guide the formulator in the determination of the design space.

This full QbD approach has been implemented for complex oral solid dosage forms, such a multi-layer tablets or tablet-in-tablet, at several contract development and manufacturing organizations. Using a tableting instrument with high speed rotary press mimicking features, the so-called compaction simulator, allows design of robust formulations, smooth scale-up, and reduced risks and costs, ultimately accelerating the time to market.

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Improving Nanoprecipitation Control

Nicola Tirelli

ROMOLO TAVANI/SHUTTERSTOCK.COM

The performance of nanoparticles used as carriers in drug delivery is intimately linked to their physical properties. Nanoprecipitation is a common method for the preparation of drug-loaded polymer nanoparticles, but the reproducibility of the two primary dimensional descriptors—the average particle size and the breadth of the size distribution—has been a challenge due to the intrinsic variability of batch processes. Microfluidics-based flow techniques, however, reduce variation in drug-loaded polymer nanoparticle synthesis.

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Targeted nanoparticle-based drug delivery has been a subject of interest for more than 20 years, and it offers a number of benefits over conventional treatment options. Encapsulation of an API in a carrier particle can protect it from degradation and allow its dispersion into an aqueous environment—the body—where typical APIs are poorly soluble. Furthermore, targeting groups can be used to address specific biological settings, maximizing the efficacy of the API while reducing the dose and, as a result, the potential for side effects.

Important goals in nanoparticle production are ensuring homogeneous particle composition, minimizing particle size distribution, and maximizing API loading. Of these, particle size distribution has arguably the most significant implications for drug delivery, because nanoparticle size determines the rate of diffusion through a tissue, and different sized particles will be taken up by cells using different mechanisms. Release of the API—either by simple diffusion or nanoparticle degradation—will also be strongly influenced by size. Smaller nanoparticles will have a greater surface area-to-volume ratio and are therefore likely to release the drug much more rapidly. This rapid release may result in high API concentrations that could potentially lead to harmful side effects. Consequently, a broad size distribution means poor control over how the API is released, making it harder to determine whether or not the patient is receiving the required therapeutic dose. This lack of control is driving the demand for production methods that reduce polydispersity.

Batch nanoprecipitation

Nanoprecipitation is the most common method for obtaining particles less than a micron in diameter. Industrially feasible production techniques have traditionally relied on a three-stage process: dissolution of a hydrophobic polymer in a water miscible solvent, mixing of this organic phase with an aqueous solution, and precipitation of the polymer. Conducting the precipitation in the presence of surfactants—or using polymers that in themselves are surfactants—preventing polymer aggregation, and co-dissolving the API in the organic phase in the first instance leads to its encapsulation within the nanoparticles.

Batch processes have typically offered the benefit of producing a large volume of material in a short period of time, as well as being conceptually easy to assemble. One-pot pouring or dropwise addition of the organic phase to the aqueous solution is the standard technique for nanoprecipitation, yet this simplicity is offset by a key disadvantage; it is difficult to set up or scale up a batch process with perfectly reproducible mixing. Even a trivial parameter, such as the distance between the magnetic stirrer and the point of injection of the organic phase, can have a profound effect on both the size dispersity and the average particle size.

Microfluidics-based processes

In contrast to batch processes, microfluidics-based devices offer a higher level of control, because the mixing of liquids takes place in channels of controlled size and geometry, and almost invariably under laminar flow. In a cross-shaped microfluidic chip (Asia system, Syrris), for example, the organic phase passes through a central channel and concentrates in the middle region when water is added laterally via the two remaining perpendicular and counter-flowing channels. The mixing is relatively slow, laminar, and consistent, and this reproducibility makes the nanoprecipitation process easy to replicate. Furthermore, the size of the particles precipitated can strongly depend on the aqueous-to-organic ratio, which can be controlled in a microfluidic process. Finally, the production can be scaled up by running several microfluidic chips in parallel.

The end result of this increased control is the reproducible production of homogeneous particles with a considerably narrower size distribution than most equivalent batch processes. Homogeneity not only offers clear benefits for drug delivery, it also delivers significant upstream advantages. During research and development, it is easier to rationalize biological results when one is confident of consistent particle size, and it is easier to transfer the process to a good laboratory practice or good manufacturing practice environment, which is a necessary step for clinical translation of the product.

Conclusion

The future of nanoprecipitation for drug delivery is likely to lie with flow techniques, but it is important not to downplay the role of batch processes, which are still key. The simplicity of batch techniques makes them ideal for exploring new materials or experimental conditions, and performing initial screenings without running the risk of, for example, obstructing the microfluidic channels. Once nanoprecipitation has been confirmed and refined under batch conditions, it can be transferred to a flow scheme for better reproducibility and control of the average nanoparticle diameter and size distribution.

The continued development of the ability to finely tune nanoparticles for drug delivery will remain a key objective in this growing area of research. The microfluidics-based flow technologies now available to academia and industry offer an alternative to batch processes for reproducible generation of homogenous nanoparticles and will continue to be catalysts for innovation and experimentation in the future. **PT**

RSM designation justification: clinical trial versus marketing application

The lesson learned is that regulatory agencies tend not to challenge RSM designations in clinical trial applications because they do not want to impede clinical development. Thus, unless the GMP portion of the API process is very short (for instance, where there are no chemical bond-making reactions, but just purification steps), the agency is not likely to reject the proposed RSM designation in the clinical trial application. Expectations are, however, very different as sponsors transition from clinical to commercial supply chain. The sponsor should, therefore, be prepared to provide a rationale and evidence in support of the RSM designation.

In conclusion, the CMC sections in regulatory filings should first demonstrate that the sponsor understands the science and technology used to produce the drug and can provide quality data to support statements in the application. Second, the sponsor has to show that adequate controls are in place throughout the entire process and that at no point in the supply chain are patients put at risk.

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High Throughput Screening of Excipients

Amjad Alhalaweh

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The author discusses the advantages of high-throughput screening of drug formulation excipients by a fully automated Tecan-robotic system.

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During early drug development, compounds have to be characterized for their toxicology, bioavailability, pharmacokinetics (PK), and pharmacology profiles. To carry out characterization studies, the compound must be dissolved in solution at a concentration that is high enough to achieve a therapeutic effect. Low aqueous solubility can, therefore, be a major challenge in drug development.

Current methodologies

Methods to improve solubility include chemical modifications, physical modifications, and solvent modifications. The method selected will be based on the compound's chemical properties, the physical state of the formulation, and the route of administration. In the development of liquid formulations, solvent modifications and carrier systems are most commonly used because they affect only the solvation characteristics of a drug rather than its solid-state properties.

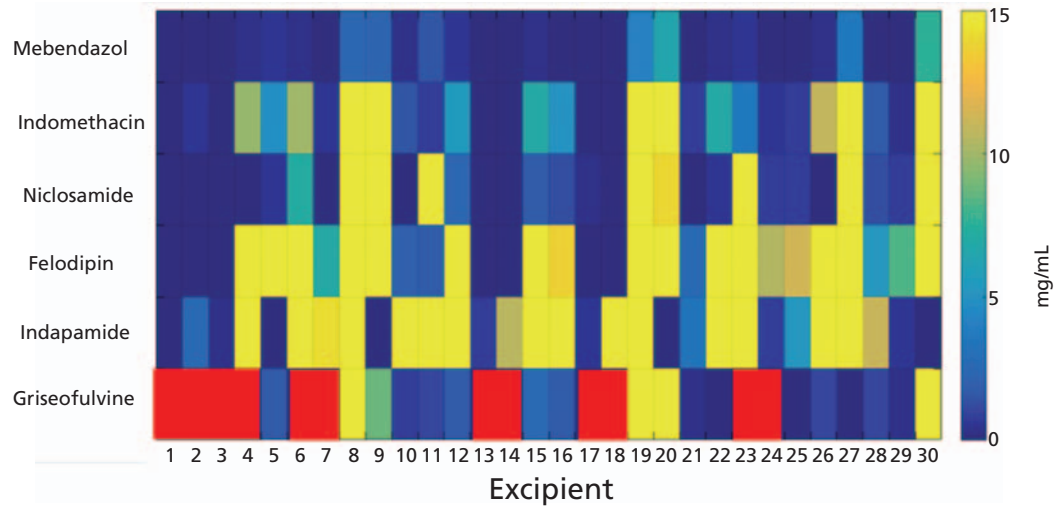
Excipients can be used to optimize the solubility of poorly soluble compounds. Traditionally, the selection of excipients relies on a trial-and-error-based approach involving a number of research-based methodologies to determine the ideal excipients. Although often successful, in reality, this approach is time-consuming, costly, and demands large amounts of material.

Developing a high-throughput screening method

A high-throughput screening method has been established to overcome the challenges of selecting one or more excipients. The aim was to develop a methodology that would use minimal amounts of API, while providing a cost-effective and efficient way to achieve results. It was also a prerequisite to establish a platform that could provide conclusive information about a compound's chemical stability in varying solvents and excipients.

Several experiments were performed to establish the methodology. The screening list involved excipients with varying solubilization mechanisms, including water-sol-

Figure 1: Solubility of the drugs in the excipients. 15 mg/mL was set as the maximum amount, with degradation of the drug indicated in red.



uble organic solvents, non-ionic surfactants, water-insoluble lipids, organic liquids/semi-solids, cyclodextrins, and phospholipids.

The type of excipients used will depend on the drug delivery system. Orally administered compounds, for example, will require different excipients than injectables. There is also a need to ensure that the final concentration of the selected excipients is within the generally recognized as safe (GRAS) list of recommended concentrations. The identification of the correct excipient in its individual correct maximum concentration is important, especially for parenteral formulations, because doses that are too high can cause pain, hemolysis, or inflammation.

A new methodology

The high-throughput screening platform is based on identifying the solubilization capacity of each excipient for a compound. It can also shorten the time taken to identify an excipient by allowing multiple tests to be performed simultaneously.

The method was initially developed using six commercially available drugs (see **Figure 1**) with diverse chemical properties. Testing was conducted using 30 excipients dispensed in 96 well-plates via a fully automated robotic system (Tecan). Three plates were studied for each compound. The plate was shaken for 48 hours to achieve equilibrium. The results were compared with solubility measurements performed using a manual shake flask method where 15 mg of powder and 2 mL of excipient were added. The samples were again shaken for 48 hours, centrifuged, and then analyzed by high-performance liquid chromatography (HPLC) to determine solubility and detect any degradation. The measurements were performed in triplicates.

Findings

Some excipients have been shown to offer better solubilization capacity than others; the trend varies between compounds (see **Figure 1**). For ionizable compounds, pH-dependent solubility is a useful approach, especially if it can be combined with another solubilizing excipient. The contribution of solid-state barrier to solubilizing a compound appears to be more pronounced at a cut-off level of solid-state properties. Before this cut-off, the solubilization of the compound was more compound specific, which creates the need to also test on a larger set of excipients.

The results of the high-throughput screening method demonstrate that solubility using this technique is not statistically different than that achieved when using a manual approach. The method can provide information on the solubilization capacity of compounds in different excipients, while also offering insight into stability.

The high-throughput screening method overcomes the challenges associated with manual approaches by being more cost-effective and economical in the use of materials, while turning around results in three to five days per set of compounds.

Conclusion

The development of the platform has created new possibilities for reduced drug development timelines and costs. Furthermore, the information generated in the screening is useful in the later stages of formulation development. Helping to boost the probability of successful formulation, selecting excipients based on an API's unique molecular properties offers a faster process that can revolutionize the way developers evaluate the solubility of any compound. **PT**

FIGURE 1 IS COURTESY OF THE AUTHOR.

Innopharma Bets on Manufacturing 4.0

Agnes Shanley

INNOPHARMA LABS

Can an Irish analytics company and its CEO bring pharma closer to 21st-century practice?

Based in Dublin, Innopharma Labs was launched in 2009 during the heady days of FDA's Process Analytical Technology (PAT) initiative, when advocates of modern process control and industrial engineering predicted a major shift in the industry's approach to quality control and manufacturing.

Years later, a full-scale shift may not have yet occurred, but concepts such as continuous manufacturing and pharmaceutical quality by design (QbD), and a redefinition of process validation, have begun to drive new, more modern approaches to drug development and manufacturing with an increasing number of approvals implementing these principles. Moving beyond its foundation in PAT and particle size imaging, Innopharma has responded by branching out into new areas that include automated process control, services, and education.

In January 2018, the company formally launched a new advanced manufacturing program based on the concept of predictive control, permitting "self-guided" granulation and sophisticated control of modified-release oral solid dosage forms. Enabling this move was a €13-million investment in Smart FB, a suite of technologies that include a data historian and cloud-based data repository, to allow manufacturers to achieve the benefits of more advanced process control for batch processes. The technology can be test driven at the company's new dedicated process R&D facility in Dublin.

Company founder and CEO Ian Jones discussed these initiatives and industry trends with *Pharmaceutical Technology*. While Innopharma is focused on the pharmaceutical industry, particularly formulation and manufacturing, it also serves the chemical, food processing, and solids processing sectors, and this knowledge informs the company's technology platform. Jones will be discussing Manufacturing 4.0 at INTERPHEX 2018 in April.

Exploring self-guided granulation and coating

PharmTech: When did you launch your advanced manufacturing pilot program and are you currently working with any industry partners?

Jones: We officially launched the pilot program in January 2018, after testing it with pharmaceutical companies during 2017. This work builds on the application development and

sensor system integration with partners Glatt, a specialist in fluidized bed drying, and Colorcon, which focuses on formulation materials including coating.

PharmTech: Are you working with any academic partners?

Jones: Over the past seven years, we have collaborated broadly with academia for PAT, but decided to invest in hiring process scientists, engineers, and chemometricians and bring this expertise inhouse. Based on input from pharmaceutical manufacturers, we have also developed our own Smart FBX advanced development and manufacturing modular platform incorporating PAT sensors, data integration engine, secure data storage, analytics and automated control components.

One-stop shopping for automation

PharmTech: Why did you feel this was necessary? After all, can't companies currently source the individual technologies (e.g., data historians and process control platforms) separately, themselves?

Jones: We felt that it was important to bring everything together. As mergers and acquisitions have become the norm in pharma, companies are managing a more diverse and global network of manufacturing sites than ever before, and contract manufacturing organizations (CMOs) are becoming a more prominent part of these networks. Our goal is to provide process data visibility, and to enable global access to development and manufacturing data so that we can support process development projects, wherever in the world they are based. Where companies lack in-house resources, our staff can step in and help with development and control problems.

PharmTech: Why do you see advanced control as being so important to pharma's future?

Jones: Just consider a car or cell phone from 15 years ago and compare them to what exists today. They are almost completely unrecognizable. A high level of advanced analytics and diagnostics has been built into these devices which has become standard in these industries, but this is not yet the case for pharma.

If the pharmaceutical industry wants to develop and manufacture safer and more affordable medicines faster, improved automation and process control will be key enablers. That's why we've gone down this road. At this point, the goal is not to pioneer, but merely to start to catch up to what other industries are doing with automation and analytics.

Smarter control will be especially crucial for scaleup and tech transfer. More, and better, technology is needed to support this work in the pharma industry.

PharmTech: What do you see as being responsible for pharma's conservatism?

Jones: The main reasons are financial and regulatory. Today, the basic focus is on doing more with what you have, rather than investing in new technology. There is also an understandable conservatism to moving away from the traditionally accepted regulatory path in case of delay to approval or a request for significant additional data for a variation submission. As a result, it has been a major challenge for tech providers and the industry to get to a stage where advanced manufacturing is even possible.

Continuous manufacturing has been a great eye opener for many pharma companies, because it has helped them understand the potential role that feedforward and feedback process control might play in their operations. Quality experts at pharmaceutical companies often see moving from batch to continuous as being too risky, so the groups leading continuous manufacturing projects are typically those charged with starting a new process for a new product. Nevertheless, as more companies support the continuous concept, even at a very limited level, it is opening the door for them to accept more innovation, especially in automation.

PharmTech: Are you currently working on continuous projects with clients?

Jones: We've worked on continuous since 2009. Advocates for continuous processing predict that 2% of all pharmaceutical products will be made that way by 2020. Companies are moving ahead with continuous, and all the major equipment suppliers are offering platforms but the industry isn't jumping as quickly as many people expected it to at first.

PharmTech: Is Smart Batch a response to these issues?

Jones: Yes, in a sense we have stepped back. We still see continuous as pharma's future, but for the present, why not retrofit existing batch processes, using the algorithms and controls that are needed to make them smarter?

PharmTech: How would Smart Batch fit in to process development, or is it mainly for manufacturing?

Jones: There is no standard approach to control for process development. Everyone is trying to figure out how to optimize development to get to market as quickly as possible and meet QbD requirements with a risk-based approach to design of experiments (DoE). Fluidized bed processes tend to have a higher regulatory risk profile for chemical, manufacturing and control (CMC) strategy, so we are working on a systematic approach.

But automated control is much more relevant during product commercialization. Algorithms can react to various permutations in the process to bring automated dynamic process control, but nobody has gone on that journey yet, and we're trying to figure it out. Customers clearly need to make batches smarter, however.

Getting closer to 'hands off' manufacturing

PharmTech: How do self-guided coating and granulation processes work?

Jones: They bring 'hands off' manufacturing closer to reality, using PAT to track critical process parameters and the product's critical quality attributes during processing. Then, they use a model to control the process phase changes, including endpoints, automatically.

In addition, the technology is being developed so that these processes can be monitored remotely in real time from anywhere in the world, even, potentially, from a smart

phone. In time, advanced manufacturing will facilitate real-time release and continuous processes.

Manufacturers around the world are supporting more automation and greater visibility of data, with many pharmaceutical companies developing and evolving plans for Pharma 4.0. There are considerable opportunities to increase manufacturing efficiency and regulatory compliance by implementing elements of Manufacturing 4.0. Improved control coupled with real-time process analytics provides process operators and supervisors with critical real-time information and reduces the risk of data transcription errors or deliberate falsification.

Primary focus on fluid bed coating and drying

PharmTech: Why did you choose to focus on fluidized-bed (Wurster) coating and drying first, and why is control important to these unit operations?

Jones: First, fluidized bed coating is a multi-step process with potential for considerable variability, for example, due to raw material variation. Even where product is within specifications, bead size can change from batch to batch. Microcrystalline cellulose, for instance, is a natural material, so measurable qualities will vary, leading to varying process results. These variations impact product quality. Fluidized bed drying can also be difficult to control, which can have a big impact on the final product quality if the optimal level of moisture content is not achieved

PharmTech: How does that variability affect the quality of finished product?

Jones: Let's consider Wurster coating. A typical pharma manufacturer will use a fixed amount of coating material, assuming that the beads are all the same size. But if you add the same amount of coating material each time, even a 20- to 30-micron difference in the size of individual bead diameters will result in different coating levels on the beads which will impact the product performance as measured by dissolution profile.

So we are applying PAT concepts to coating to help ensure fixed particle size change so that users can get the same coating characteristics every time, despite variability in raw materials and other factors. This approach uses advanced manufacturing principles.

First, the Eyecon analyzer is used to measure the initial particle size at the start of processing. The initial size data is automatically fed to a dynamic process-control algorithm that we've developed inhouse. That algorithm defines the trajectory needed to add the correct amount of material per minute to achieve to required coating thickness and stops the process once it has reached a predefined growth level.

The platform will be useful for developmental work, because it complements DoE software and allows product development teams to program and schedule development batches and access time aligned process and PAT sensor data such as PSD, moisture, spray rate, atomization pressure, air flow, temperature etc. on demand. Operators can then run the experiments, collate data, and run a sequential experiments. After each batch, users can access data to see how that batch did, and, after all runs are complete, they will be able to compare data and transfer key data to the DoE analysis tool. The platform makes definition of a design space and development of a process control strategy more efficient and makes data required for technical justification more accessible.

Jumping forward to controlling a commercial-scale batch, this setup would allow users to determine the optimal bead growth rate and terminate underperforming batches to ensure that rate is achieved.

Dissolution prediction would also be a crucial capability, but we will have to partner closely with each customer to determine the best approach, since every formulation will involve unique challenges (e.g., whether using water based or solvent based coatings, or different levels of API).

We will be focusing on fluidized bed coating for the next two years, and haven't yet decided what the next step will be.

As the industry becomes more comfortable with remote data access, users would be able to view data via smartphone, laptop, or tablet using a 21 *Code of Federal Regulations* (CFR) Part 11-compliant data structure.

Incorporating the Internet of Things

PharmTech: How does this platform embrace the concept of the Internet of Things?

Jones: Through its use of process equipment sensors and additional PAT sensors for critical process parameter and quality attribute measurements, cloud-based architecture and artificial intelligence, in the form of dynamic process control and the use of algorithms, and, ultimately through remote data access. We have talked with nine out of the 10 Big Pharma companies that use PAT extensively, and their feedback was very positive. We've also had positive feedback from equipment vendors, and the regulators are open to facilitate the adoption of new technologies. FDA appears to be leading the field with its most recent Pharmaceutical CMC Guidelines, "*Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization Guidance for Industry*."

PharmTech: Are you focusing on one single equipment vendor or a limited number?

Jones: We will continue our long standing collaborationwith one vendor (Glatt), but expect to be able to retrofit to any customer's or vendor's equipment.

PharmTech: You had recently launched training and educational programs. What are your plans in that area?

Jones: As well as up-skilling thousands of students each year, we are in the process of launching our new online education program. It will first be available only in the European Union, but by the third quarter of this year, will be accessible from anywhere in the world.

This program fits in with our contract services in validation and scale-up support, which we introduced 18 months

ago. Pharmaceutical manufacturers often have difficulty filling positions in these areas because there aren't enough people with the right skills and experience to handle formulation development, scaleup, and manufacturing. With FDA's new process validation guidance, there is a need for continuous process verification and the skills and technology required to support that effort.

Another focus for us, in both training and services, is project management. We have taken people without any pharma experience (e.g., professionals who have worked in the electronics industry) and given them 500 hours of validation and project management training and experience and found that they perform very well when placed into (bio)pharma environments.

PharmTech: Are you working in biologics?

Jones: At this point, we are focused on small molecules. In addition to our work in pharmaceuticals, we are also very active in the food and chemical industries, where we have worked on processes for infant formula and industrial solids materials. The experience is extremely applicable to oral solid-dosage form manufacturing, where there has been a real uptake in interest in automated control over the past three to four years.

PharmTech: What impact is outsourcing having on the way that pharmaceutical monitoring and automation solutions are being developed?

Jones: It's hard to impose technology on a service provider. A contract manufacturer will generally make product with whatever tools the sponsor provides and supplement with support for process critical gaps identified during tech transfer planning. But the virtual company, Vertex Pharmaceuticals, has given the industry a great example of what is possible when the right tools are provided, in particular, for analytics and control.

Remote data visibility in real time has huge potential to improve outsourcing. One of the industry's greatest challenges is the fact that, due to restructuring, the repositories of manufacturing knowledge aren't there anymore. As a result, gaining real-time data visibility is very powerful. If a batch isn't performing properly, this visibility allows you to react and intervene right away. As a result, we are getting some very positive responses from CMOs. Meanwhile, sponsors are using analytical technologies to profile processes at old sites and replicate them in new ones.

PharmTech: Your company came into being during the years following FDA's PAT initiative. How fully has the industry adopted PAT?

Jones: I prefer to take a 20-year perspective on PAT. Back in the earliest days, before the FDA initiative, some people were using the concept and spending a lot on it, but they didn't fully understand what they wanted it to do and how it would help them develop and control a process.

In addition, the technologies they were using had come from other industries and were not as fit for purpose as they might have been for pharma. For example, an analyzer might have been good for measuring cement but not the particle size diameters found in pharma excipients. In addition, much of the early equipment lacked compliance capability for pharma applications. Then along came the FDA guidance, which may have brought too much rigor to the implementation approach. The whole initiative seemed to go quiet for about 10 years.

Over the past five years, however, we have seen a renaissance in process analytical technologies. People understand the guidelines better and are more comfortable with them, and the industry is more mature in its approach to buying the technology that is required. At the same time, technology providers have invested a considerable amount of money in making their equipment fit for purpose in pharma, in particular, developing better, more user-friendly interfaces for pharma. We're seeing much greater use of PAT for measuring moisture content and particle size for powder processes, and it is finding greater use in tech transfer. More generic-drug manufacturers are also using it.

Addressing gaps in the short term

PharmTech: Where do you see advanced manufacturing going in pharma in the short term?

Jones: It's too early to tell, but there are already many initiatives in development to implement QbD principles to develop more defined, better understood processes. Efforts are increasing to apply automation, at least for end point control of critical process steps, often by combining process equipment sensors and PAT sensors to develop more sophisticated control. These are important early steps on the journey toward fuller automated process control.

One wonders what Elon Musk might do if he were to explore pharma. How would he get the molecule to the patient? The question is whether disruptive technologies will allow pharma to reach true patient-centered care and circumvent the *status quo*. Only time will tell, but we hope that our efforts will stimulate new thinking and help answer some fundamental questions. **PT**

Ad Index

CPhI north america

2018 PLANNING GUIDE

CPhI North America and Pharmaceutical Technology *are UBM plc brands.*

Bioprocessing Zone informEx P-mec ICSE InnoPack FDF

CPhI Returns to Philadelphia

The entire pharma supply chain is reunited and charged to do business at CPhI North America 2018 in Philadelphia, PA on April 24–26.

Joseph Marks
Brand Director,
CPhI North America

Following up on last year's remarkably successful inaugural event, CPhI is again bringing its influential infrastructure to the most progressive pharmaceutical market on Earth, North America! Happening April 24–26 in Philadelphia, PA, more than 7400 pharma power players and more than 630 of today's most innovative suppliers will descend upon the Pennsylvania Convention Center to show you the incredible power of our connective community.

CPhI North America is pulling out all the stops with prominent industry leaders, powerhouse companies, and an educational program that's more immersive than ever before. You won't just attend CPhI North America; you'll leave with actionable insights, indispensable professional contacts, and lucrative new partnerships.

So, what's in store for 2018?

Much More Than an Expo Hall—It's Your Marketplace

CPhI North America's expo hall is where the magic happens. At 93,500 sq. ft., we added two new product zones this year, making it the most expansive marketplace to connect buyers and sellers at every stage of the purchasing process and supply chain. This year's zones are:

- *CPhI*: Manufacturing Ingredients Zone
- *InformEx*: Fine & Specialty Chemicals Zone
- *FDF*: Finished Drug Products Zone
- *iCSE*: Drug Development Zone
- *Bioprocessing*: Biopharmaceuticals Zone
- *InnoPack*: Packaging Zone
- *P-MEC*: Machinery Zone

Conference program spotlights innovation in a new era of regulation

Only in this year's Conference Connect Program will you unlock access to all the insights shaping the future of pharma and bio-pharma, focused through the lens of more than 25 esteemed speakers forging new frontiers in our industry. To strategically address the industry-driving changes, we partnered with the American Chemical Society (ACS), US Pharmacopeial Convention (USP), and Life Sciences Pennsylvania (LSPA) to bring you three days packed with more than 40 hours of sessions rooted in trending industry subject areas of drug development, drug manufacturing, and biomanufacturing.

Big names, bigger ideas: Visionary keynote speakers

This year's headliners offer the perfect mix of education and motivation; revolutionary presentations will help you stay one step ahead of our evolving industry. Our visionary featured keynotes include The Medical Futurist, Bertalan Mesko, and Jeremy Frank, vice-president of digital medicine platform development at Proteus Digital Health. They're ready to take the stage and embark on a captivating journey that will show you how science-fiction technologies and digital medicines are transforming healthcare as we know it.

Career-changing connections

Through it all, you'll have ample networking opportunities and unprecedented access to your peers, speakers, and influencers at the Opening Welcome Reception, the Women in Leadership Forum, and other galvanizing gatherings throughout the show.

If you haven't already registered, go to CPhINorthAmerica.com and get your pass today. Next stop: Philadelphia. See you there!

CPhI North America

April 24–26, 2018
Pennsylvania Convention Center
Philadelphia, PA USA

Education Sessions
- CPhI North America Conference
- Insight Briefings
- Exhibitor Showcases
- Innovation Gallery

Networking
- Opening night welcome reception
- Women in Leadership Forum
- BOND: Networking Meeting Service

Register
www.cphinorthamerica.com

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Network, Learn, and Connect

CPhI North America offers a range of networking, educational, and exhibition opportunities for bio/pharma industry professionals to develop technical, business, and professional expertise in drug development and manufacturing.

Welcome Reception

Tuesday, April 24, 2018, 6–8 pm
CPhI North America will host a welcome reception at the historic National Constitution Center, which is located at 525 Arch St., Philadelphia. The Welcome Reception is open to attendees holding VIP Attendee, Conference, and Exhibitor passes.

Educational Sessions

The CPhI North America Conference features sessions focused on drug development, drug manufacturing, bioprocessing, and quality and regulatory issues led by experts from the bio/pharma industry, contract services, and supplier community. In keynote sessions, thought leaders will share their visions and experiences of how technology innovations can improve the patient experience. See pages CPhI 5–8 of this Planning Guide for more information.

Exhibitor Showcases

Exhibitor Showcases are concise, insightful presentations delivered by the leading solution providers on the CPhI North America exhibition floor. These presentations are accessible to all exhibition visitors. See page CPhI 18 of this Planning Guide for more information.

Insight Briefings

Insight Briefings are in-depth seminars on technical and business topics held on the CPhI North America exhibition floor. They are accessible to all exhibition visitors. Topics include the contract services market dynamics, supply chain issues, serialization, and more. See page CPhI 18 of this Planning Guide for the latest schedule.

Registration

CPhI North America offers registration options to fit visitor schedules and agendas. See cphinorthamerica.com/badge-options for details. Use the code "PHARMTECH" to get an additional $50 off Conference and VIP passes.

Travel

The Pennsylvania Convention Center, located at 1101 Arch Street, Philadelphia, is accessible by taxi, car, or public transportation. Visit http://cphinorthamerica.com/travel-info for more information.

CPhI Women in Leadership Forum

Thursday, April 26, 8:00–11:30 am
The CPhI Women in Leadership Forum brings together female executives from across the global pharma network to share experiences, trade knowledge, and build a community of like-minded individuals. Hear strategies for leadership and advice on overcoming workplace challenges from industry speakers. Make new contacts and network in a relaxed environment.

8–8:30 am: **Breakfast and Networking**

8:30–8:35 am: **Welcome from the Chair**

8:35–9:05 am: **Keynote**

9:05–10:10 am
Panel Discussion and Q&A: Empowering Women to Thrive
How can you leverage your support systems to realize your potential? Topics include:

- Mentoring—helping each other to succeed
- Corporate strategies and company culture
- Self-empowerment—What can you do to create your own opportunities?
- Paying it forward

10:10–11 am
World Café (A dynamic networking space)
Join group discussions to share your questions and experiences, and those of your peers and panel members.

11–11:30 am: **Coffee and Networking**

Schedule subject to change. Passes for this event can be purchased via the Register link on www.cphinorthamerica.com.

Hotels: CPhI North America has designated Convention Housing Partners (CHP) as the official hotel provider for 2018. Visit www.cphihotels.com for discounted rates at hotels close to the venue.

CPhI North America Events as of Feb. 9, 2018. Visit cphinorthamerica.com for schedule updates.

Monday, April 23, 2018

Time	Event	Location
2 pm–6 pm	Registration Open	Pennsylvania Convention Center, 100 Level Foyer

Tuesday, April 24, 2018

Time	Event	Location
7:30 am–6 pm	Registration Open	Pennsylvania Convention Center, 100 Level Foyer
9:30 am–12:30 pm	CPhI North America Conference Presentations	Pennsylvania Convention Center, 100 Level Meeting Rooms
10 am-5 pm	CPhI North America Expo Hall Open	Pennsylvania Convention Center, 200 Level
10:30 am–1:30 pm	Insight Briefings	Insight Briefings Theater, Exhibition Hall, 600 Aisle
10:30 am–1:30 pm	Exhibitor Showcases	Exhibitor Showcase Theater, Exhibition Hall, 1800 Aisle
1:30–2:15 pm	Keynote Address: Science Fiction in Healthcare *Bertalan Mesko, Director of The Medical Futurist Institute*	Pennsylvania Convention Center, 100 Level Meeting Rooms
2:15–5 pm	CPhI North America Conference Presentations	Pennsylvania Convention Center
2:30–5 pm	Insight Briefings	Insight Briefings Theater, Exhibition Hall, 600 Aisle
2:30–5 pm	Exhibitor Showcases	Exhibitor Showcase Theater, Exhibition Hall, 1800 Aisle
6–8 pm	Welcome Reception (Open to all badge types excluding Expo Only)	National Constitution Center

Wednesday, April 25, 2018

Time	Event	Location
8 am–5 pm	Registration Open	Pennsylvania Convention Center, 100 Level Foyer
9:30–12:30 pm	CPhI North America Conference Presentations	Pennsylvania Convention Center, 100 Level Meeting Rooms
10 am–5 pm	CPhI North America Expo Hall Open	Pennsylvania Convention Center, 200 Level
10:30 am–1:30 pm	Insight Briefings	Insight Briefings Theater, Exhibition Hall, 600 Aisle
10:30 am–1:30 pm	Exhibitor Showcases	Exhibitor Showcase Theater, Exhibition Hall, 1800 Aisle
1:30–2:15 pm	Keynote Address: Proteus Digital Health *Jeremy Frank, Vice-President of Digital Medicine Platform Development, Proteus Digital Health*	Pennsylvania Convention Center, 100 Level Meeting Rooms
2:15–3:45 pm	CPhI North America Conference Presentations	Pennsylvania Convention Center
2:30–5 pm	Insight Briefings	Insight Briefings Theater, Exhibition Hall, 600 Aisle
2:30–5 pm	Exhibitor Showcases	Exhibitor Showcase Theater, Exhibition Hall, 1800 Aisle
3:45–4:30 pm	Contract Services Yesterday, Today, and Tomorrow: A Retrospective with Jim Miller	Insight Briefings Theater, Exhibition Hall, 600 Aisle

Thursday, April 26, 2018

Time	Event	Location
8 am–3 pm	Registration Open	Pennsylvania Convention Center, 100 Level Foyer
10 am–5 pm	CPhI North America Expo Hall Open	Pennsylvania Convention Center, 200 Level
10:30 am–1:30 pm	Insight Briefings	Insight Briefings Theater, Exhibition Hall, 600 Aisle
10:30 am–1:30 pm	Exhibitor Showcases	Exhibitor Showcase Theater, Exhibition Hall, 1800 Aisle
1:30–2:15 pm	Keynote Address	Pennsylvania Convention Center
2:30–3 pm	Insight Briefings	Insight Briefings Theater, Exhibition Hall, 600 Aisle
2:30–3 pm	Exhibitor Showcases	Exhibitor Showcase Theater, Exhibition Hall, 1800 Aisle

Explore Pharma Issues in Depth

Education tracks explore the latest trends in drug development, drug manufacturing, and bioprocessing.

Drug Development Track

Tuesday April 24, 2018
9:30 am–9:45 am
Opening Remarks by Drug Development Track Chairperson
Rita Peters, editorial director, Pharmaceutical Technology, *UBM*

9:45 am–10:30 am
Detecting Potential Formulation Roadblocks in Early Drug Development
Panel discussion moderated by *Pharmaceutical Technology*
Getting a compound to clinic is a milestone in the development of a drug. However, formulation hurdles or cost-prohibitive manufacturing challenges detected in later development stages can delay—or derail—the development and approval of a promising compound. Can the odds for getting a drug to market be improved by troubleshooting formulation challenges during early development phases? A panel of experts will review tools, strategies, and methods for assessing the formulation, drug delivery, and manufacturing potential of a drug candidate in preclinical phases. Implications for timelines, API materials, and budgets will be discussed.
Moderator: Rita Peters, editorial director, Pharmaceutical Technology
Panelists to be announced

Tuesday April 24, 10:30 am–11:15 am
Fostering Precompetitive Collaborations on New Enabling Technologies for Pharmaceutical Research and Development
Powered by American Chemical Society (ACS)
As the pharmaceutical industry explores new ways to stimulate innovation, reduce costs, and streamline operations, precompetitive cross-pharma collaborations on the development of new research technologies have become increasingly attractive. Recent efforts directed at joint development of enabling technologies for discovery and development will be presented, along with case histories and success stories illustrating the value of this joint development approach.
Christopher J. Welch, chief scientific officer, Welch Innovation, LLC

Tuesday April 24, 11:45 am–12:30 pm
Precision Medicine/Cell & Gene Therapies—The Changing Paradigm of Manufacturing Fireside Chat
Powered by Life Sciences Pennsylvania (LSPA)
Leading biopharma companies have nearly doubled their investment in personalized medicine in the past five years and expect an additional 30% increase over the next five years. The manufacturing science and development for new innovations such as CAR-T therapies and gene therapies faces challenges of efficiency, scalability/sustainability, and cost of goods. Hear about the outlook for precision medicine and its impact on manufacturing science and product/process development.
Moderator: Christopher P. Molineaux, president and CEO, Life Sciences Pennsylvania
Panelists:
Usman (Oz) Azam, president and CEO, Tmunity Therapeutics
Patrick Dentinger, president and CEO, Absorption Systems
Alan Moore, commercial chief of biologics, WuXi AppTec

Keynote Addresses

Tuesday April 24, 2018, 1:30 pm–2:15 pm
Science Fiction in Healthcare
Bertalan Mesko, director of The Medical Futurist Institute and Amazon Top 100 author, will detail how science-fiction technologies can become reality in medicine and healthcare. His futuristic presentation will discuss embracing disruptive medical technologies, putting patients in the center of healthcare, digitizing healthcare information, and shifting focus from treatment to prevention.
Bertalan Mesko, The Medical Futurist

Wednesday, April 25, 2018, 1:30 pm–2:15 pm
Advances in Digital Medicine
Proteus Digital Health is commercializing a new category of therapy: digital medicines. These offerings include widely used drugs, formulated so they communicate when they have been swallowed; a wearable patch that detects medicines and captures physiologic response; mobile applications to support patient self-care and physician decision-making; and data analytics to serve the needs of health system managers. Jeremy Frank discusses how his teams develop integrated medication with sensors, wearable patches, and physiologic algorithms.
Jeremy Frank, vice-president of digital medicine platform development, Proteus Digital Health

Tuesday April 24, 2:15 pm–3 pm
Solubility Enhancement and Improving Oral Bioavailability–Panel Discussion
Poorly water-soluble molecules account for approximately 70–90% of molecules in R&D pipelines. Enabling technologies to improve solubility can increase the chances that poorly soluble compounds will successfully reach the patients who need them. A panel of experts will address how to use the appropriate technology selection early in development; how to select the right technologies to increase the solubility and bioavailability of poorly soluble compounds; and stability and scale-up challenges.
Moderator: Jennifer Markarian, manufacturing editor, Pharmaceutical Technology, *UBM*
Panelists:
Brian Anderson, director, drug products, AbbVie Operations
Traciann Scirbona, process engineer, Hovione
Hibreniguss Terefe, vice-president, R&D, ExxPharma Therapeutics

Tuesday April 24, 3 pm–4:30 pm
Hot-Melt Extrusion Challenges and Solutions
Experts from three companies explain the use of hot-melt extrusion (HME) to develop amorphous solid dispersions (ASDs) to improve solubility of drug products.

Part I: Hibreniguss Terefe, vice-president, research and development, ExxPharma Therapeutics reviews the importance of understanding the drug substance, formulation, and HME process parameters in the development of ASD-based drug products.

Part II: Anna VanDyke, senior sales manager, AbbVie, describes the company's efforts to develop, scale-up, and commercialize challenging chemical entities using a proprietary HME technology.

Part III: Traciann Scirbona, process engineer, Hovione, explains how a screening process that uses minimal amounts of the API can resolve formulation issues on laboratory-scale equipment, and then scale up to meet manufacturing requirements.

Part IV: Catalent Pharma Solutions

Wednesday, April 25, 2018
9:30 am–9:45 am
Day 1 Recap/Day 2 Overview
Rita Peters, editorial director, Pharmaceutical Technology, *UBM*

Wednesday, April 25, 9:45 am–10:30 am
Advances in API Synthesis/Scale-Up, Part I
Powered by American Chemical Society (ACS)
During these case study driven sessions, experts will discuss API synthesis and best practices for scale-up.
Speakers to be announced

Wednesday, April 25, 10:30 am–11:15 am
Technology and Formulation Selection for Bioavailability Enhancement
Powered by American Chemical Society (ACS)
This session will review potential barriers to absorption and low bioavailability, compound properties, dose, pharmacokinetics; and a model-based approach. Suitable technology options, *in-vitro* tools, and a right-first-time approach for performance, manufacturability, and stability will be discussed.
David Vodak, head of research and development, drug product development and innovation, Lonza

Wednesday, April 25, 11:45 am–12:30 pm
Toxicology Strategies for Drug Discovery: Personal Thoughts
Powered by American Chemical Society (ACS)
This session will examine the impact of nonclinical safety-related attrition on pharmaceutical R&D productivity, including the significance for different types of molecules and how a realistic nonclinical safety-related attrition rate can be achieved. Front-loading toxicity testing, physicochemical properties, and *in-vitro* and computational toxicology tools will be reviewed.
Eric Blomme, vice-president global preclinical safety, AbbVie

Wednesday, April 25, 2:15 pm–3 pm
Accelerated Stability Assessment Program (ASAP): Fast Determination of Drug Product Shelf-Life
The session will describe an accelerated stability assessment program that features a combination of studies and mathematical/statistical analysis to determine drug product shelf-life in just three weeks. The system has been used by pharmaceutical companies to speed product development, including formulation selection, process development, and packaging selection.
Ken Waterman, president and founder, Free Think Technologies, Inc.

Wednesday, April 25, 3 pm–3:45 pm
Fixed-Dose Combination Drugs: A Cost-Effective Approach for Simplified Dosing
Fixed-dose combination products (FDCs), which contain multiple active ingredients, offer benefits to both patients and drug companies. The 505(b)(2) pathway is commonly used for these approvals as most of the FDCs usually consist of previously approved drugs, which leads to smaller development programs. Producing safe and effective FDC products requires thoughtful product design, access to state-of-the-art manufacturing technology, and advanced analytical tools. This session will feature case studies of FDCs highlighting both adult and pediatric formulation development and innovation, and processing challenges associated with development of FDCs.
Anthony Qu, vice-president scientific affairs, Halo Pharmaceutical

Drug Manufacturing Track

Tuesday April 24, 2018
9:30 am–9:45 am
Drug Manufacturing Track Chairperson's Opening Remarks
Feliza Mirasol, science editor, Pharmaceutical Technology *and* BioPharm International, *UBM*

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Tuesday April 24, 9:45 am–10:30 am
One Process from Milligrams to Kilograms; Efficient Drug Substance Development Enabled by Continuous Manufacturing Technology
Powered by American Chemical Society (ACS)
The nature of continuous manufacturing creates new opportunities for efficient and single-cycle process development. The use of automated, well-characterized lab reactors with tight control over process parameters and rich data collection are enabling new ideas in chemical process development. Lab reactors designed to accurately model production reactors facilitate efficient development of continuous manufacturing processes. Examples of this scale-by-design process development will be presented, with emphasis on reaction types for which flow technology is truly enabling.
Matthew M. Bio, president and CEO, Snapdragon Chemistry, Inc.

Tuesday April 24, 10:30 am–11:15 am
High Potency Drug Manufacturing–Controlling Manufacturing Quality and Containment
Given the cross-contamination and containment risks highly potent APIs (HPAPIs) present, manufacturing and handling approaches must be carefully considered. This session will examine process validation considerations and scale-up in HPAPI production; strategies for effective management of HPAPI supply chain; best practices for cleaning validation; and specific requirements for processing of antibody-drug conjugates.
Speakers to be announced

Tuesday April 24, 11:45 am–12:30 pm
Continuous Processing Technologies for API and Intermediate Manufacturing: Innovation Meeting Market Demand
Continuous processing of APIs and intermediates can resolve manufacturing issues arising from today's more complex therapies including improved safety and sustainability, easier scale-up, and lower operating costs. In this session, continuous versus traditional batch processing will be compared. Benefits of smaller batch sizes, less solvent use, control of parameters during a reaction, use of custom microreactors, and greater control of unstable reactions will be reviewed.
Sam Tadayon, executive director, process engineering, STA Pharmaceutical

Tuesday April 24, 2:15 pm–3 pm
Live with Michael Levy, Head of Research & Innovation at USP: The Role of Quality Standards in Emerging Technologies
Powered by USP
The very nature of medicines and the technologies used to develop, manufacture, deliver, and test them are continuously evolving. Ensuring that patients have access to quality-assured medicines requires that quality standards also evolve. The paradigm of release testing small molecular weight medicines with traditional approaches will have to shift to account for ever more complex treatments that are produced in new ways, assessed differently, and at different times. This session will provide an overview of some of the work being done at USP to address these questions and ensure the availability of quality medicines.
Michael Levy, vice-president and head, USP Quality Institute and Head of Research and Innovation, USP

Tuesday April 24, 3 pm–4:30 pm
Regulatory Considerations, Strategy, and Best Practices for Choosing a Quality Contract Manufacturing Organization
New drug development presents a myriad of challenges, particularly when choosing to work with a contract manufacturing organization (CMO). Critical decisions will ultimately affect your ability to produce a therapeutic agent that delivers high quality results on time and on budget. This session will review questions to ask and how to assess competencies of potential CMO partners to ensure a drug company's needs are met across the spectrum of compliance, production, quality, communication, and more.
Bryan J. Coleman, senior director pharmaceutical and device consulting services, EAS Consulting Group

Tuesday April 24, 4:15 pm–5 pm
Risk Management in Technology Transfer
Technology transfer serves as the link between drug/API development and manufacturing; a successful transfer depends on the evaluation and management of risk to complete the project on time with predefined quality and cost. This presentation will provide ways to achieve the objective of "right-at-first-time-technology transfer" including the use of cross-functional teams. The discussion covers chemical process development, analytical method development, equipment selection, safety risk assessment, quality and GMP risk assessment, plant process validation, and regulatory filings.
Shyam B. Vispute, general manager–tech transfer, Neuland Labs

Wednesday, April 25, 2018
9:30 am–9:45 am
Day 1 Recap/Day 2 Overview
Agnes Shanley, senior editor, Pharmaceutical Technology, *UBM*

Wednesday, April 25, 9:45 am–10:30 am
Excipient Innovation and its Impact on Drug Development, Part I
Excipient innovation is becoming increasingly important as the current available pharmaceutical excipients will not be able to adequately address formulation issues—solubility, permeability, taste masking, stability—and manufacturing challenges—including continuous manufacturing and 3-D printing—in the future. Panelists will review novel excipients, the role of co-processed excipients, the current regulatory landscape for the adoption of novel excipients, and efforts by IQ Pharmaceutical Consortium and IPEC-

Americas to accelerate excipient innovation by engaging with FDA to define a more appropriate regulatory pathway in the future.
Panelists: Nigel Langley, director technical service and scientific affairs, BASF Pharma Solutions
Joe Zeleznik, manager of technical affairs, MEGGLE USA

Wednesday, April 25, 10:30 am–11:15 am
Excipient Innovation and its Impact on Drug Development, Part II
Panelists from IPEC-Americas and the IQ Consortium will discuss the issues identified in Part I, and ask the audience about driving needs for novel excipients, hurdles that may prevent the use of novel excipients, and ways to facilitate innovation and the use of novel excipients to resolve formulation and production problems or enhance quality and productivity.
Panelists: Nigel Langley, director technical service and scientific affairs, BASF Pharma Solutions
David Schoneker, director of global regulatory affairs, Colorcon, Inc
Joe Zeleznik, manager of technical affairs, MEGGLE USA

Wednesday, April 25, 11:45 am–12:30 pm
Best Business Practices (Or Lack Thereof) and Legal Challenges with Indian Contract Research and Manufacturing Outsourcing: How Not to Remain Sleepless with India Pharma Services Outsourcing
This session will review best business practices and legal challenges with Indian contract research and manufacturing services and will give an overview of Indian pharmaceutical research and manufacturing outsourcing services and key vendors. Topics to be addressed include business practices, cultural differences, legal landscape, regulatory compliance, US jurisdiction for Indian companies, tax issues, contract laws, and dispute resolution.
Ram Balani, CEO and founder, FDASmart Inc.

Wednesday, April 25, 2:15 pm–3 pm
The Role of Quality Verified Ingredients in the Global Supply Chain
Powered by USP
Supplier qualification programs are designed to address concerns regarding ingredient quality; however, complex, and global supply chains, combined with resource constraints, can inhibit the finished product manufacturer's ability to qualify suppliers. Third-party verification of ingredients can help ensure ingredient quality and reduce the risk of inconsistent and substandard quality in the finished product. This session will review how the USP ingredient verification programs can help manufacturers free up resources to address other critical quality risks.
Stephen W. Andruski, senior manager, USP

Wednesday, April 25, 3 pm–3:45 pm
Innovative Quality by Design Approach to Continuous Manufacturing
Speakers to be announced

Bio-Processing Symposium

Wednesday, April 25, 2018
9:30 am–9:45 am
Opening Remarks, Bio-Processing Symposium Chairperson

Wednesday, April 25, 9:45 am–10:30 am
Future Outlook for Bioprocessing
This presentation will provide a big picture outlook on emerging trends, new technologies, and the future market forecast for bioprocessing.
Speakers to be announced

Wednesday, April 25, 10:30 am–11:15 am
A Molecule's Journey—Breaking Down Roadblocks to Commercial Success
Every biopharma executive must make important decisions early in clinical development that will impact their molecule's journey, and ultimately the success of their commercial strategy. The key to this success is to make the right decisions at the right time. In this presentation, an expert will share some key considerations to help biopharmaceutical companies successfully advance a molecule from the laboratory to the clinic as quickly as possible without sacrificing product quality, process efficiency, or patient safety. To achieve this goal, companies must navigate the complexities associated with business planning, cell line development, process development, technology, and regulatory and risk assessment.
Guillaume Plane, marketing and development, process solutions, Merck Millipore S.A.S.

Wednesday, April 25, 11:45 am–12:30 pm
USP Standards to Support Qualification of Raw Materials and Cell Substrates for Biomanufacturing
Powered by USP
The quality of starting materials is crucial for successful pharmaceutical manufacturing strategies. For biomanufacturing, the challenges are amplified due to the use of a variety of raw materials, cell lines, and naturally-derived materials with an increased risk for the introduction of unwanted impurities and adventitious agents. This presentation will provide an overview and updates on USP documentary standards containing best practices for qualifying incoming materials, demonstrating viral clearance, cryopreservation, cell banking, and controlling impurities derived from cell substrates for therapeutic proteins.
Maura Kibbey, director, global biologics, USP

Wednesday, April 25, 2:15–3 pm
Cell Line Development and New Technologies
Speakers to be announced

Wednesday, April 25, 3 pm–3:45 pm
Case Study–Implementing Novel Technologies to Reduce Timelines
Speakers to be announced

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Exhibitors Represent Global Pharma Supplier Market

More than 630 companies will be featured in the CPhI North America exhibition hall.

Exhibit Hours

Tuesday, April 24, 2018: 10 am–5 pm
Wednesday, April 25, 2018, 10 am–5 pm
Thursday, April 26, 2018: 10 am–3 pm

Connect with Solutions Providers

CPhI North America's BOND: Exclusive Meeting Service is designed to facilitate connections between solutions seekers and providers based on compatible needs and capabilities. See cphinorthamerica.com/events-features for more information.

This exhibitor list contains information as of Feb. 22, 2018. For updates, see www.cphinorthamerica.com.

Visit *Pharmaceutical Technology* at Booth 1862.

EXHIBITOR NAME	BOOTH #
3M Drug Delivery Systems	1365
A&C American Chemicals Ltd	628
A.H.A International Co., Ltd.	561
Aavis Pharmaceuticals	1711
AB BioTechnologies, Inc.	1714
Abacipharm Corp	1650
AbbVie	1219
abcr GmbH	1151
Ablaze Glass Works Pvt. Ltd.	165
Ace Glass	413
Acebright Group	1207
Aceto Corporation	913
ACG North America LLC	1132
Aconitum	1165
Adare Pharmaceuticals, Inc.	1125
Adesis Inc.	1362
Aenova	1537
AGC Biologics	1707
AGC Chemicals Americas Inc.	200
AGI USA, Inc.	224
Agno Pharma	1245
AIC	813
Aktin Chemicals, Inc.	585
Albemarle	419
Alcami	801
Alconox Inc.	1529
Alivira Animal Health - Sequent Group	279
Alliance Technologies, Inc.	1925
Allychem Co., Ltd.	427
Almac Group Ltd.	524
Alpex Pharma SA	1923
Althea	1703
Amano Enzyme USA Co. Ltd.	1509
Ambiopharm Inc.	1006
Amcor Flexibles Americas	2105
American Chemical Society (ACS)	1749
American Cleanstat	1628
American International Container	936
American Renolit Corp. LA	2021
Amindon, Inc.	300
AminoLogics Co., Ltd.	1458
Aminowill Wuxi Jinghai Amino Acid Co., Ltd.	1143
AMRI	301
Amsyn Inc.	310
Angelini A.C.R.A.F Spa	950
Anhui Biochem United Pharmaceutical	534
Anhui Heryi Pharmaceutical Co., Ltd.	438
Anmol Chemicals	373
Anqiu Lu'an Pharmaceutical A510	1247
Apex Aseptic Products	206
Aphena Pharma	1532
Aptar Pharma	2104
Arbes Tools Pvt. Ltd.	2036
Ark Pharm Inc	314
Artisan Industries Inc.	236
Ashland Inc	372
AST LLC	2041
AstaTech (Chengdu) BioPharmaceutical Corp.	962
Astatech Inc.	1732
Asymchem, Inc.	1439
Atabay	360
Aurisco Pharmaceutical Co., Ltd.	849
Austin Chemical Company Inc.	701
Avanti Polar Lipids, Inc.	933
Avara Pharmaceutical Services	1307
Avema Contract Services	1636
Avista Pharma Solutions, Inc.	1536
Axcellerate	1329
Azico Biophore India Pvt. Ltd.	302
B&W Tek	1612
Bachem AG	661
Baiyu Pharmaceutical, Co., Ltd.	1261
BANGKOK BOTANICA	1157
Baxter Biopharma Solutions	1445
BCN Peptides SA	1229
BCPP	1257
BD	1632
Beijing Huikang Boyuan Chemical Tech.	589
Beijing Odyssey Chemicals Co., Ltd.	431
Beilite Chemical Co., Ltd.	484
Bellen Chemistry	1450
Bellwyck Pharma Services	1237
Benzo Chem Industries Pvt. Ltd.	850
Berkshire Sterile Manufacturing	1927
Berry Plastics	1924
Biazzi SA	138
Biddle Sawyer Corporation	663
Bioduro	1462
Biological E Ltd.	1032
Biopeptek Pharmaceuticals	1804
Biophore Pharma Inc.	711
BioSpectra	625
Biotechpharma UAB	1904
Biovectra Inc	632

Contin. on page CPhI 12

The People and Science Behind

Patheon OneSource™ for Small & Emerging Pharma

MOLECULE TEAMS

2400+ scientists ready for your challenge

The Drug Substance Molecule Team collaborates with the Drug Product Team to ensure that your molecule becomes a formulation-ready API. The integrated Molecule Team is a key driver of the Patheon OneSource™ time savings.

Andreas Stolle, Ph.D., joined us in 2015
Vice President, API Process Development Services

DRUG SUBSTANCE PROJECT MANAGER

560+ development programs in 2016

Whether you are working with a large molecule or a small molecule, your Drug Substance Project Manager proactively works to ensure your molecule has its best shot at success by maintaining timelines and minimizing potential rework during development.

Angela Colarusso, joined us in 2007
Sr. Director, Biologics Program and Proposals Management

Patheon OneSource™ Program Manager

SOURCING TEAM

Smart sourcing
Procurement experts assist with sourcing generic API and raw materials to ensure availability and reliable supply.

ADMINISTRATION

Simplified administration
If it works better for your business, we can establish one Master Service Agreement, one Drug Substance/Drug Product Contract and one Quality Agreement. This also means one taxation and regulatory structure, one currency and one invoicing process.

Faster Drug Development

We develop 75% of all dosage forms

For large and small molecules, close collaboration with the Drug Substance Molecule Team allows the application of right-fit science for formulation, process development, tech transfer and scale-up to ensure a smoother transition to market.

Anil Kane, Ph.D., MBA, joined us in 2000
Executive Director, Global Head of Technical & Scientific Affairs

CLINICAL TRIAL MANUFACTURING

112 NDA approvals in 10 years

More than 2x any other CDMO

For both large and small molecules, the Patheon OneSource™ methodology minimizes failures due to foreseeable events and maximizes your molecule's chances of out-licensing or making it to market.

DRUG PRODUCT PROJECT MANAGER

Stability and scalability

By collaborating with the Drug Substance Project Manager, the Drug Product Project Manager ensures your trial-level drug product is also suitable for scale-up.

Nicky Arvanitis, MBA, joined us in 1997
Director, PDS Project Management

CLINICAL PACKAGING AND DISTRIBUTION

Securely packaged for on-time distribution

Combining best-in-class robust primary and secondary clinical packaging and secure on-time distribution to meet quality standards and patient compliance.

BACK-UP PROGRAM MANAGER

We always have a back-up plan

To ensure your molecule never goes off track, every team includes a Back-up Program Manager ready to step in any time life gets in the way.

Save an average of 14 Weeks & $44.7M[1]

Something needs to be done about the high cost of drug development. By combining drug substance, drug product, clinical manufacturing and clinical packaging into a single process, Patheon OneSource™ accelerates your molecule like nobody else can.

Speed through communication

The Program Manager is the architect of your drug development program. This single point of contact both within Patheon, and with you, simplifies every interaction and manages your molecule's critical path to deliver unmatched time and cost savings.

Aaron Williams, PMP, joined us in 2011
Program Manager, Patheon OneSource™

Patheon part of Thermo Fisher Scientific | OneSource™

www.patheon.com/onesource

1. Assessing the Financial Benefits of Faster Development Times: The Case of Single-Source vs. Multi-Vendor Outsourced Manufacturing, Tufts Center for the Study of Drug Development, 2017

Contin. from page CPhI 9

EXHIBITOR NAME	BOOTH #
Bloomage Freda Biopharm USA, Inc.	1028
Bona Pharma	2022
Bormioli Pharma	2001
Boron Molecular Inc.	233
Bosch Packaging Technology, Inc.	2233
Brand-Nu Laboratories/Yabang-QH	937
Brandwidth Solutions	1638
Brenntag Specialties	927
BSP Pharmaceuticals S.p.a.	1501
Budenheim	1160
Busch Vacuum Pumps and Systems	2100
Calgon Carbon Corporation	160
Callery, LLC	553
Cambrex	613
Cambridge Isotope Laboratories, Inc.	564
Capot Chemical Co., Ltd.	638
Caregen Co., Ltd	1101
Cascade Custom Chemistry	508
Catalent Pharma Solutions	1401
CCCMHPIE	159, 381, 535, 584, 586, 1461, 1837, 1906, 1935, 1936, 2121, 2222, 2229
CelesTech, Inc.	1148
CellMark USA, LLC	952
Central Glass Corp.	309
Cerbios	701
Changzhou GenChem & GenPharm Pharmaceutical Co., Ltd.	832
Changzhou Juyou New Material Tech Co., Ltd.	181
Changzhou LonGo Chemical Co., Ltd.	583
Changzhou Sunlight Pharmaceutical Co., Ltd.	424
Charkit Chemical Corporation	828
Chartwell Actives	1043
Chemada/Icl-Ip	140
ChemCon GmbH	648
Chemglass Life Sciences	239
Chemical Information Services Inc.	332
Chemical Solutions Ltd.	1456
Chemlex Pharmaceuticals	129
Chempacific Corporation	439
Chempartner/China Gateway	453
Chemtour Biotech	753
Chengdu Apothe Laboratories Ltd.	344
Chengdu Biopurify Phytochemicals, Ltd.	1805
China Synchem Technology Co., Ltd.	486
Chiral Technologies Inc.	364
Chongqing Carelife Pharmaceutical Co., Ltd.	765
Ciron Drugs & Pharmaceuticals Pvt Ltd.	1232
Civentichem	465
CMIC CMO USA Corporation	1313
Colorcon Inc	1937
Comar LLC	662
Comi Polaris Systems, Inc.	409
Contipro A.S.	471
Contract Pharma	1815
Contract Pharmacal Corp.	1625
Contract Pharmaceuticals Limited Canada	1144
Coral Drugs Pvt. Ltd.	1311
Coral LLC	1153
Corden Pharma International	1432
CoreRx	1433
Corning Incorporated	114
Corning Sas	313
CPC Scientific Inc.	472
CPhI NA	1465
Crystal Pharmatech	1652
CSIRO	233
CurTec USA, Inc.	733
Custom Granular Inc.	228
Cyalume Specialty Products	1037
Cymtek Laboratories, Limited	558
Dalchem	552
Dalian Join King Fine Chemical Co. Ltd.	464
DanYang WanLong Chemical Co., Ltd.	1613
Dastech International, Inc.	932
Datwyler Pharma Packaging USA.	2004
DCS Pharma USA	1050
Deseret Laboratories	235
DFE Pharma	1333
DIA Pharmaceutical Co., Ltd.	1337
Digital Specialty Chemicals	336
Divi's Laboratories Limited	543
Dorizoe Lifesciences Ltd.	1833
Dottikon Exclusive Synthesis	505
Dow Chemical Corporation	1019
DPL-US (A division of Dr. Paul Lohmann Inc.)	1045
DPT	1513
Drugdu Technology	1624
DSL Chemicals (Shanghai) Co. Ltd.	204
DSM	1635
Dupont Nutrition and Health	827
DWK Life Sciences Inc.	2017
DZD (Heze) Pharm	537
EAS Consulting Group LLC	856
Eastar Chemical Corp.	208
Eastman Chemical Company	760
Edelmann USA	2012
Ei LLC	1325
Ekato Corporation	255
ELC Group	1945
EMBOCAPS by Suheung	705
Emergent Biosolutions	1238
EquipNet Inc.	308
Erbozeta S.p.A.	1250
ESIM Chemicals GmbH	448
Esteve Quimica S.A.	338
Eurofins Alphora	1535
Eurofins Lancaster Laboratories, Inc.	1533
EuTech Scientific Services, Inc.	1452
eVenus Pharmaceutical Laboratories, Inc.	1059
Evonik Corporation	748
Exergy, LLC	2045
F.P.S. Food and Pharma Systems Srl	1637
Famar SA	1825
Far Chemical Inc	551
Fareva	649
Federal Equipment Company	513
Feihe Chemical Co., Ltd.	842
Fermion Oy	1149
Fine Organics Ltd.	370
Finoso Pharma	1934
First American Equipment Finance	352
Flamma Spa	610
Flow Sciences, Inc.	542
Fluorotech USA	550
Foster Delivery Science	265
Fresenius Kabi Product Partnering	836
Frontida BioPharm	1201
Fuji Chemical Industries	736
G. M. Chemie Pvt. Ltd.	1152
Gansu Nuokeda Trading Co., Ltd.	430
Gelest Inc.	1052
Generichem	953
Genibet Biopharmaceuticals, SA.	1741
Genovior Biotech Corp.	1715
Gentec Pharmaceutical Group	958

EXHIBITOR NAME	BOOTH #
GEO Specialty Chemicals	271
Gerresheimer AG	2008
Gesellschaft für Micronisierung mbH	529
GFS Chemicals Inc.	410
GHW-USA	150
GL Filtration Limited	1734
Grand River Aseptic Manufacturing	1801
Graphic West Serialization and Packaging	2217
Graver Technologies	219
GreenBiochem LLC	149
Grifols International, S.A.	1437
Groupe Parima	1137
GSK/GlaxoSmithKline	1407
Guangdong Raffle PharmaTech Co., Ltd.	113
Gujarat Organics Ltd.	470
GVK Biosciences	1700
Haemopharm Healthcare s.r.l	2117
Hainan Guoning Import & Export Co., Ltd.	126
Halo Pharmaceutical, Inc.	1549
Hamari Chemicals Ltd.	951
Hangzhou Allsino Chemicals Co., Ltd.	387
Hangzhou Minsheng Binjiang Pharmaceutical Co., Ltd.	742
Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd.	1244
Hebei Chengxin Co., Ltd.	339
Hebei First Rubber Medical Technology	1947
Hebei Jianmin Starch Glucose Co., Ltd.	533
Hebei Jiheng (Group) Pharmaceutical	1320
Hebei Yanuo Bioscience Co., Ltd.	479
Heinkel Group USA	1539
Helsinn Advanced Synthesis SA	749
High Hope Int'l Group Jiangsu Medicines and Health Products Imp & Exp Corp Ltd.	845
HighChem America Inc.	1457
Hisun Pharmaceuticals USA, Inc.	1025
Hovione PharmaScience	624
HTL S.A.S.	366
HuaJian Service US	1736
Hubei Gedian Humanwell Pharmaceutical.	959
Hubei Goto Biotechnology Co., Ltd.	844
Hunan Hanrui New Material Technology.	256
Hybio Pharmaceutical Co., Ltd	1265
I-Chess	666
Ideal Cures Pvt., Ltd.	637
IDT Biologika gmbH	1406
ILC Dover	1701
IMCD US Pharma	1036
Impopharma, Inc.	1460
InCon Process Systems LLC	411
Inhale Health	1912
Innophos Inc.	205
Insight Finechem Co., Ltd.	1060
Integrated Analytical Laboratories	1338
IntelGenX Corp.	1453
Interchem Corporation.	650
IPEC Americas	634
International Speciality Chemicals and Pharmaceuticals	261
Intertek	1601
Inventys Research Company Pvt., Ltd.	354
Iofina Chemical Inc.	460
IRA Istituto Ricerche Applicate	528
IRISYS Pharma Development, Manufacturing & Regulatory Solutions	1929
Italian Trade Agency	1719
Italian Trade Agency	1719b
J&W Pharmlab LLC	1359
Jaytick Chemicals Inc.	304
JenKem Technology Co., Ltd.	530
Jiangsu Hanbon Science & Technology Co.	1829
Jiangsu Jiaerke Pharmaceuticals Group	1348
Jiangsu Maida New Material Co., Ltd.	258
Jiangxi Sunway Chemical Co., Ltd.	559
Jiangxi Time Chemical Co., Ltd.	957
Jiaozuo Zhongwei Special Products Pharmaceutical Co., Ltd.	569
JM Rodgers Co., Inc.	1705
Johnson Matthey	536
Jost Chemical Co	837
JRS Pharma	1242
J-Star Research Inc.	231
Jubilant HollisterStier.	1611
Kerry	1159
Kewpie Corporation	861
Kikkoman Biochemifa	578
Kingchem Life Sciences LLC	333
KinOmega Biopharm Inc.	203
Kodak Specialty Chemicals	761
Lablabo	2119
Laboratório Medinfar-Produtos Farmacêuticos, S.A.	1741
Laboratórios Azevedos - Indústria Farmacêutica, S.A.	1741
Laboratórios Basi-Indústria Farmacêutica	1741
Lacamas Laboratories Inc.	633
Lauda-Brinkmann Lp	229
Laurus Synthesis Inc.	459
Laviana Pharma Co., Ltd.	435
LCI Corporation	365
LGC Standards	1614
Lgm Pharma	901
Liaoyuan Silver Eagle Pharmaceutical	656
Life Sciences Pennsylvania	1543
Lifecore Biomedical, LLC	636
LinkChem Co., Ltd.	1542
Lipoid, LLC	467
Livzon Group Ningxia New North River Pharmaceutical Co., Ltd.	1145
Log Plastic Products Co., Ltd.	2018
Lonza Pharma & Biotech	605
Louisiana Chemical Equipment Company	334
Luna Chemicals Co., Ltd.	1436
Lyophilization Technology, Inc.	1553
M.O. Industries	2027
Macco Organiques, s.r.o.	853
Macleods Pharmaceuticals Ltd	737
Malladi Drugs & Pharmaceuticals Ltd.	273
Mallinckrodt Generic Division	1225
Materia, Inc.	549
Mcgean	408
Medpack Swiss Group	1264
Mercachem-Syncom Group	701
Meroven Pharmaceuticals	1065
Metrics Contract Services	1424
Metro Exporters Pvt,. Ltd.	478
Mfg Chemical Inc.	137
Micronclean	2023
Midas-Care Pharmaceuticals Pvt Ltd	266
MilliporeSigma	619
Minakem	371
Minsheng Group Shaoxing Pharmaceutical	744
Morepen Laboratories Ltd.	501
Morre-Tec Industries Inc.	213
MPD Chemicals	325
MPP Group LLC	1941
MRIglobal	1428
MSU Bioeconomy Institute	405
MyGen Pharmaceuticals Inc.	573
NAL Pharmaceutical Group Limited	1233
Nanjing Chemical Material Corp.	252

EXHIBITOR NAME	BOOTH #
Nanjing Chemlin Chemical Industry Co., Ltd.	572
Nanjing Dorra Pharmaceutical Technology	1228
Nanjing Guochen Chemicals Co., Ltd.	280
Nanjing Lifenergy R& D Co., Ltd.	1443
Nantong Sane Biological Co., Ltd.	574
Nation Ford Chemical Company	401
Navin Fluorine International, Ltd.	249
Nectar Lifesciences Ltd.	267
Neopharm Labs	1239
Neostar United Changzhou Industrial	560
Neuland Laboratories	732
New Chemic (U.S.) Inc.	264
Nexus Company Inc.	2125
Niacet Corporation	135
Nipro Pharmapackaging International	2225
Nitta Gelatin NA, Inc.	665
Nobel Pharmaceuticals	1033
NOF Corporation	579
Norquay Technology Inc.	327
Novasep	449
Novo Nordisk A/S	927
Oakwood Chemicals	215
Oceanic Pharmachem Pvt., Ltd.	833
Okchem Inc.	1712
Olon Spa	1544
OMPI	2204
One Source Biopharma, LLC	125
Optima Chemical and Optima Belle	725
Orbis Biosciences	1933
Organic Technologies	1361
Orion Corporation	1248
Ortec Inc.	412
Pace Analytical Life Sciences, LLC	1324
PAMAS USA	1551
Park Systems	2133
Patheon	1001
Paul O Abbe	407
PCAS	565
PCI Pharma Services	601
PCI Synthesis	1552
Pennakem	454
Perry Videx LIc	312
Pet Flavors Inc.	575
Peter Greven US Corporation	1260
Pfanstiehl	1235
Pfizer CentreOne	1213
Pharma Portugal	1741
PharmaBioSource Inc.	1243
PharmaBlock USA, Inc.	1142
Pharmaffiliates Analytics & Synthetics	1349
Pharmagra Labs, Inc.	759
PHARMAnetwork sarl	1835
PharmaResources (Shanghai) Co., Ltd.	532
Pharmasol Corporation	1633
Pharmax NA Inc.	511
Pharmco-Aaper	232
Phoenix Equipment Corporation	356
Phosphonics Limited	905
PHT International Inc.	1057
Pierre Fabre CDMO	357
Pii Pharmaceutics International Inc.	554
Piramal Pharma Solutions	504
Polpharma Pharmaceutical Works	1049
PolyCine GmbH	2000
Polycrystalline	1556
Polymer Chemistry Innovations Inc.	1360
PolyPeptide Group	1004
Polysciences Inc.	848
Porocel International LLC	259
Power Container Corp.	2207
PPD	1560
PQE US, Inc.	1806
Precision NanoSystems Inc.	2232
Pressure Chemical Co.	456
Procaps SA	1301
Purolite	821
Pyramid Laboratories, Inc.	1901
Q Laboratories	1351
Qi-Chem Co., Ltd.	428
Qilu Pharmaceutical Co., Ltd.	719
Qingdao Jiulong Biopharmaceutical Group	1058
Qingdao Kangyuan Pharmaceutical Co., Ltd.	1056
Qingdao Kingwish Int'l Co., Ltd.	379
Qosina	2005
Qualicaps, Inc.	1413
QuickLabel	2116
Quotient Sciences	1339
RA Chem Pharma Limited	1224
Raymat - AVF	961
Reachlaw Ltd.	353
Recro Gainesville LLC	1252
Regis Technologies Inc.	115
Reine Lifescience	570
Reliance Label Solutions	250
Ricerca Biosciences	1544
Richman Chemical	510
Rieke Metals, LLC	457
Robatel Inc.	1357
Rohner Inc.	443
Rommelag	1605
Rommelag FLEX	1605
Ropack Inc.	1919
Roquette	1007
Rousselot, Inc.	253
Rovi Contract Manufacturing S.L.	1438
Rovipharm	2216
Roy + LeClair	2209
Royal Chemical Company	330
R-Pharm Germany GmbH	1449
RxTPL	1558
S.I.F.RA. EST S.p.A	2014
SA Traders	358
Safebridge Consultants, Inc.	1328
SCHOTT Pharmaceutical Systems	2020
Senn Chemicals AG	757
Sentinel Process Systems, Inc.	210
Seppic Inc.	1026
Servier CDMO	1507
sfm Medical Devices USA	2205
SGS Life Sciences	1334
Shandong Huimeng Bio-tech Co., Ltd.	128
ShanDong Kexing Bioproducts Co., Ltd	1346
Shandong Kunda Biotechnology Co., Ltd	324
Shandong Lixing Chemical Co., Ltd.	133
Shandong Luoxin Pharmaceutical Group Hengxin Pharmaceutical Co., Ltd.	556
Shandong Pharmaceutical Glass Co., Ltd.	2028
Shandong Topscience Biotech Co., Ltd.	342
Shandong Xintai Water Treatment Technology Co., Ltd.	385
Shandong Xisace New Materials Technology Co., Ltd.	1121
Shanghai AQ BioPharma Co., Ltd.	278
Shanghai Bayuechemicals Co., Ltd.	432
Shanghai Chemspec Corporation	500
Shanghai Forxine Pharmaceutical Co., Ltd.	473
Shanghai HeGeng Biotech Engineering	1928
Shanghai Nucleosides Bio-Technology	658
Shanghai Pharma Group Changzhou Kony Pharmaceutical Co., Ltd	964
Shanghai Rich Chemicals Co., Ltd.	378
Shanghai Ruiyi Medical Tech Co., Ltd.	337
Shanghai Yuking Water Soluble Material Tech Co., Ltd.	1220

EXHIBITOR NAME	BOOTH #
Sharp Packaging Solutions	1800
ShedirPharma S.r.l	1158
Shenzhen Oriental Pharmaceutical Co., Ltd.	1048
Shiseido Co., Ltd.	568
Shouguang Fukang Pharmaceutical Co.,Ltd	434
Shulan City Jinma Chemical Co., Ltd.	481
Sichuan Huafamei Enterprise Co., Ltd.	270
Siegfried	1256
Sigachi US Inc.	1053
SiliCycle Inc	219
Siltech Corporation	512
Simagchem Corp	238
Singota Solutions	1336
Sino High Goal Chemical Technology Co., Ltd.	745
Sinochem Hebei Fuheng Co., Ltd.	179
Sinochem Jaingsu Co., Ltd.	1258
Sinocompound Catalysts Co., Ltd.	557
SK biotek	1448
SL Pharma Labs, Inc.	1608
Snowbell Machines Pvt. Ltd.	2044
Society of Chemical Manufacturers & Affiliates (SOCMA)	119
SoftGels	1410
Solvay	474
Solvias AG	960
Sourcechem Co., Ltd.	429
Sovereign Pharmaceuticals, LLC	1550
Spectrum Chemical Mfg. Corp.	211
Speed Laboratory Inc.	1932
STA Pharmaceutical	519
Sterling Pharma Solutions	1648
Strem Chemicals Inc.	112
Strongarm Designs, Inc.	2032
SuanFarma	136
Sulzer Mixpac AG	1710
Sun Pharmaceutical Industries Inc.	1412
Suparna Chemicals, Ltd.	548
Surmount Laboratories Pvt Ltd.	1364
Survival Technologies Pvt. Ltd.	1013
Sutphin Drugs Inc.	1606
Suven Life Sciences	349
Suzhou Highfine Biotech Co., Ltd.	1249
Swiss Parenterals Pvt. Ltd.	1136
SwRI	1326
SX Pharma	657
Symbiotica Speciality Ingredients SDN BHD	1164
Sympatec Inc.	2019
Syngene International	643
Taiwan Kimax Controls Inc.	143
Taixing Yangzi Pharm Chemical Industry Co., Ltd.	245
Takasago International Corporation	348
Tatva Chintan USA	157
TC Scientific Inc.	212
TCG Lifesciences	131
Tci America	152
Technoflex	2010
Tecoland Corporation	209
Teh Seng Pharma	1156
Tergus Pharma	1332
tesa Labtec GmbH	1342
Textron Technica SLU	907
The Dharamsi Morarji Chemical Co., Ltd.	251
Tianjin Chengyi International Trading Co.	124
Tianjin Jiateng Chemical Products Co., Ltd.	254
Tianjin Jinjin Pharmaceutical Co., Ltd.	1218
Tianjin Minxiang Biomedical Inc.	1119
Tianjin Tianyao Pharmaceuticals	1425
Tiarco Chemical	359
TMC Industries, Inc.	1353
Topharman Shanghai Co., Ltd.	475
Toronto Research Chemicals Inc.	1039
Tosoh USA Inc.	214
Trecora Chemical	148
Tyger Scientific Inc.	153
Umicore AG & Co. KG	225
Unichem Enterprises	452
Unipharma LLC	1525
Unither Pharmaceuticals	1133
Univar Pharma Ingredients	858
UPM Pharmaceuticals	1519
UPM Raflatac	2126
US Pharmacopeial Convention (USP)	1649
Vacuubrand Inc.	437
Valliscor	201
Vandemark Chemical Inc.	525
Vanderbilt Minerals LLC	445
Vasudha Pharma Chem Ltd.	1062
Vefa Ilac	1253
Vertellus	248
Viakem, S.A. De C.V.	355
Vikram Thermo India Ltd.	852
Vinchem, Inc.	1619
WAB US Corporation	2237
Ward/Kraft, Inc.	328
Web Talent Marketing	1344
Wego Chemical Group	455
Weihai Disu Pharmaceutical Co., Ltd.	1318
West Pharmaceutical Services	1812
WeylChem International GmbH	329
Wilmington Pharma Tech Co. LLC	331
Wisesorbent Technology LLC.	2040
WR Grace	571
Xi'an Gaoyuan Bio-Chem Co., Ltd.	539
Xiamen Goodhealth Pharmchem Co., Ltd.	764
Yacht Biotechnology Co., Ltd.	436
Yamasa Corporation	664
Yancheng City Shengda Chemical Co., Ltd.	433
Yangzhou Chemical Co., Ltd.	260
Yichang Sanxia Pharmaceuticals	1807
Yiling Pharmaceutical Inc.	1810
Yizheng East Chemical Co., Ltd.	326
Zeon Corporation	948
ZETA Pharmaceuticals LLC	1900
Zhejiang Ausun Pharmaceutical Co., Ltd.	865
Zhejiang Charioteer Pharmaceutical Co., Ltd.	425
Zhejiang Chemicals Import & Export Corporation	843
Zhejiang Guobang Pharmaceutical Co., Ltd	1129
Zhejiang Jinhua Conba Bio-Pharm. Co., Ltd.	1107
Zhejiang Jiuzhou Pharmaceutical Co., Ltd.	1113
Zhejiang Langhua Pharmaceutical Co., Ltd.	743
Zhejiang Medicines & Health Products Import & Export Co., Ltd.	660
Zhejiang Neo-Dankong Pharmaceutical Co., Ltd.	243
Zhejiang Peptites Biotech Co., Ltd.	1459
Zhejiang Ruibang Laboratories.	942
Zhejiang Supor Pharmaceuticals Co., Ltd.	1615
Zhejiang Tianyu Pharmaceutical Co., Ltd.	949
Zhejiang Xianfeng Technologies Co., Ltd.	587
Zhenjiang Runzhou Jinshan Packing Factory	155
Zhuhai Rundu Pharmaceutical Co., Ltd.	944
Zxchem USA Inc.	1150

Location

Pennsylvania Convention Center
200 Level

Exhibit Hours

Tuesday, April 24, 2018: 10 am–5 pm
Wednesday, April 25, 2018, 10 am–5 pm
Thursday, April 26, 2018: 10 am–3 pm

Pharma Value-Chain Zones

The CPhI North America exhibition floor features more than 630 exhibitors covering all aspects of the pharmaceutical value chain. The exhibit hall is segmented into special zones:

- **iCSE**, the Drug Development Zone, features contract research organizations and other service providers serving drug developers.
- **CPhI**, the Manufacturing Ingredients Zone, features suppliers of APIs and excipients.
- **FDF**, the Finished Drug Products Zone, features small- and large-molecule contract development and manufacturing organizations.
- **InnoPack**, the Packaging Zone, showcases packaging innovation.
- The **Bioprocessing** zone features companies involved in the development and manufacture of biologic-based drugs.
- **InformEx** features suppliers in fine and specialty chemical markets.

This exhibitor floor plan contains information as of Feb. 9, 2018.
For updates, see www.cphinorthamerica.com

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Insights, Solutions, and Updates

The CPhI North America Exhibition Hall will feature presentations, interviews, and briefings on industry topics.

Insight Briefings

Insight Briefings are in-depth, 45-minute seminars on technical and business topics held in the Insight Brefings Theater in the CPhI North America Exhibit Hall. All exhibition visitors can attend for free. See cphinorthamerica.com/insight-briefings for the most current schedule and topics.

Tuesday, April 24, 2018

11:30 am: **Safebridge Consultants, Inc.**

12:30 pm: **American Chemical Society**

2:30 pm: **Amin Talati Upadhye LLP**

3:30 pm: **Pfizer CentreOne**

Wednesday, April 25, 2018

10:30 am: **Leavitt Partners**

11:30 am: **Sharp Packaging**

Special Event: Expert Q&A

Sponsored by Pharmaceutical Technology

Wednesday, April 25, 2018

3:45–4:30 pm

Insight Brefings Theater, CPhI North America Exhibit Hall

Contract Services Yesterday, Today, and Tomorrow: A Retrospective with Jim Miller

Veteran industry analyst Jim Miller, founder and former president of PharmSource, A GlobalData Company, will share his perspectives of changes in the contract services market over the past 20 years; recent shifts in the pharma development, manufacturing, distribution, and regulatory landscape; and implications for bio/pharma companies and contract services providers alike.

Exhibitor Showcases

In Exhibitor Showcases, suppliers present perspectives on their products, innovations, and services. These 25-minute, free-to-attend presentations, held in the Exhibitor Showcase Theater in the CPhI North America Exhibit Hall, provide an open platform to interact face-to-face with suppliers. See http://cphinorthamerica.com/showcases for the most current schedule and topics.

Exhibitor Showcase Schedule

Tuesday, April 24, 2018	
Time	**Event**
10:30 am	J-Star Research Inc.
11 am	Kodak Specialty Chemicals
11:30 am	DFE pharma
12 noon	Polpharma
12:30 pm	Integrated Analytical Laboratories
1 pm	Univar USA Inc.
2:30 pm	Avista Pharma Solutions
3 pm	Bachem Americas, Inc.
3:30 pm	Corning SAS
Wednesday, April 25, 2018	
Time	**Event**
10:30 am	LGM Pharma
11 am	B&W Tek
11:30 am	Pyramid Laboratories, Inc.
12 noon	Albemarle
12:30 pm	Grifols International, S.A.
1 pm	US Pharmacopeial Convention
2:30 pm	Optima Chemical/Optima Belle
3 pm	West Pharmaceutical Services
3:30 pm	Ompi
4 pm	WAB-GROUP
Thursday, April 26, 2018	
Time	**Event**
10:30 am	Lacamas Laboratories

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