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SPECIAL FEATURE - Outsourcing Formulation Development & Manufacturing: Early-Stage Partnerships Are On The Rise

The pharmaceutical industry likes to outsource. And that fact is blatantly obvious when one considers the outsourcing activity within the formulation development and manufacturing sector.

According to a 2013 report from Frost & Sullivan, on a global scale, pharma spent $13.43 billion on contract manufacturing services. That number is expected to reach $18.49 billion by 2017.

The Frost & Sullivan report indicates that injectable dose formulations will likely be the primary growth driver for outsourcing through 2017, primarily due to an increased pharmaceutical and biotechnological focus on complex disease areas.

However, in 2012, solid-dose formulations were the largest segment, constituting 49.8% of the total pharmaceutical contract manufacturing market, and is projected to grow at a CAGR of 3.4% through 2017. Generics are the key driver for growth in this segment. Liquid and semi-solid dose formulations are considered a mature market and its CAGR is expected to be only around 2.5% from 2012 to 2017. This is due to a decreasing demand for such formulations, primarily attributed to associated transportation, storage, and packaging issues.

Because of pharma's increased outsourcing practices, contract formulation and manufacturing providers are striving to provide a greater value proposition for clients by engaging earlier in projects and establishing longer-term relationships. According to Frost & Sullivan, many are focusing on pre-clinical development services and can transition from offering clinical services to commercial manufacturing to integrate throughout the value chain of clients.

Drug Development & Delivery recently asked leading CMOs and CDMOs to describe the value-added services they offer with respect to formulation and manufacturing. Solving challenges of insufficient solubility, poor stability, identifying excipient candidates, and particle design topped their list of offerings.

AAIPHARMA SERVICES CORP. & CAMBRIDGE MAJOR LABORATORIES, INC.—LINKING DRUG SUBSTANCE & DRUG PRODUCT CAPABILITIES

AAIPharma Services Corp. and Cambridge Major Laboratories, Inc. recently joined to form a comprehensive pharmaceutical development and manufacturing services supplier. With nearly 800 employees operating out of 7 sites in the U.S. and Europe, the combined capabilities include API development and manufacturing, solid-state chemistry, formulation development, analytical development and testing services, clinical and commercial finished dosage form manufacturing (solid dose and parenteral), packaging, and stability services.

"Our family of companies delivers reliable partnership and superior value to pharmaceutical, biotechnology, medical device, and generics companies by providing access to comprehensive services – from early-phase studies to commercial production of APIs and finished dosage forms," says Paul Maffuid, PhD, Exceutive Vice President of Pharma Operations at AAIPharma Services Corp. "By linking drug substance and drug product capabilities, our family of companies provides a continuous process to establish the physical properties of the drug substance (e.g. salt forms and polymorphs, particle size distribution) early to achieve the target product profile. This also ensures a smooth transition from formulation development to manufacturing, as well as ensuring consistency through clinical development."

Pharmaceutical companies bear the challenge of delivering on simultaneous objectives related to profitability, to both advance a portfolio of pipeline candidates, and also reduce operational costs. "We see increased demand for contract dosage form development and manufacturing overall, both for programmatic and transactional work, because of the efficiency gains that outsourcing provides," says Dr. Maffuid. "Outsourcing transfers to suppliers the responsibility for fixed costs associated with operating and staffing manufacturing facilities, for costs associated with adherence to regulatory guidelines, and for capital investment in technology."

In January of 2014, AAIPharma Services Corp. completed a multi-million dollar expansion of its cGMP parenteral manufacturing facility in Charleston, SC. The expansion doubled the facility's sterile product development and production capacity and added state-of-the-art redundancies to major processing equipment. New facility features include low line loss and in-line weight check capabilities.

In addition, the buildout was engineered to accommodate a pilot and production-scale SP Hull lyophilizer, which will more than triple the facility's lyophilization capacity by late 2014, and afford seamless lyophilization cycle optimization and scale-up, explains Dr. Maffuid.

In 2013, AAIPharma Services added a multi-layer tablet press, the Korsch XL 400 MFP, with a flexible design platform that permits production of all tablet formats (single-layer, bi-layer, tri-layer and corecoating) on a single tablet press.

"Many of our early-phase pharma clients are challenged with the need to meet aggressive timelines and/or overcome challenging molecular properties," he says. As an example, one client required an injectable dosage form for a Phase I study on a fast track timeline. The aggressive timeline dictated that route optimization for active pharmaceutical ingredient (API) production would occur concurrently with dosage form development activities. Before initiating formulation development, the analytical methods were evaluated and deemed stability indicating. Formulation development work was initiated with experimental material, and optimization work was required to address insufficient solubility, poor stability, and excipient restrictions specific to the target patient population. "Using available developmental grade API, AAIPharma Services developed a strategy for dissolution, pH adjustment, and oxidation protection enabling sterilization by filtration and filling prior to lyophilization," explains Dr. Maffuid. "The ability to conduct real-time analysis using stage-appropriate validated stability indicating methods in our analytical development group was essential to this effort, and within one month of release of the first lot of cGMP compliant API, AAIPharma Services was able to manufacture the first lot of Phase I product for clinical evaluation."

In another early-phase challenge, a client requested three strengths of immediate-release capsules for a blinded study using a drug development candidate with extremely poor solubility across the desired pH range, and poor wettability that resulted in processability and uniformity issues with the existing manufacturing method. AAIPharma addressed the wettability issue by incorporating a GRAS surfactant into the dry blend process, resulting in an improved dissolution rate to the target amount and ensured that the target immediate-release profile was achieved.

A third early-phase scenario illustrates how AAIPharma developed a feasible clinical approach for human evaluation of a client compound within acceptable limits for co-solvents and surfactants. In this case, the client requested the development of an injectable vehicle with a high-dose target, short lifetime, and rapid clearance rate. "While the client was able to achieve some improvement in solubility by increasing pH, it was not enough improvement to deliver a feasible dosage form, and the increased solubility came at the expense of stability," says Dr. Maffuid. "The AAIPharma solution was to develop a two-component formulation – API was dissolved in a non-aqueous vehicle consisting of GRAS solvents and surfactants, and the aqueous vehicle enabled safe IV administration with a solution that was physically and chemically stable."

AAIPharma Services offers cGMP solid oral dose and parenteral dose manufacturing capabilities, including small and large molecules with the flexibility to support early product development through commercial supply.

The AAIPharma Services team is also adept at expedited technology transfer for clinical and commercial projects. For instance, a client requested a study to understand why it was seeing low antioxidant levels in a commercial product. AAIPharma put together a plan to understand the impact of excipients on antioxidant stability. “We conducted a controlled study using materials from manufacturing inventory, replicated manufacturing conditions, and conducted support analysis for antioxidant levels at time points ranging from hours to weeks at controlled temperatures. Results were obtained within two hours of prototype vial preparation, and we demonstrated that one excipient in the formulation was responsible for the reduction in antioxidant level.”

Dr. Maffuid goes on to explain how AAIPharma has successfully leveraged technology for dosage form development and for extending patent life on existing branded products. In this scenario, AAIPharma investigated the feasibility of formulating a highly flexible drug delivery system using mini-tablets in hard gelatin capsules to deliver one or more drugs in a variety of release profiles. The feasibility of delivering a drug or multiple drug combinations in a biphasic immediate/extended-release manner was demonstrated by combining mini-tablets of various release profiles in a hard gelatin capsule. In the end, the team demonstrated that a pulsatile-release pattern is feasible with the combination of immediate-, delayed-, and extended-release mini-tablets.

Based on these various scenarios, Dr. Maffuid is convinced that outsourcing formulation development and manufacturing will continue to increase, driven by the overall trend to offset fixed costs and capital expenditure, with faster-than-market growth expected in biopharmaceutical manufacturing, biosimilars, targeted therapies, high potency drugs, and injectable dosage forms.

AGERE—A BEST-PRACTICES APPROACH TO FORMULATION & MANUFACTURING

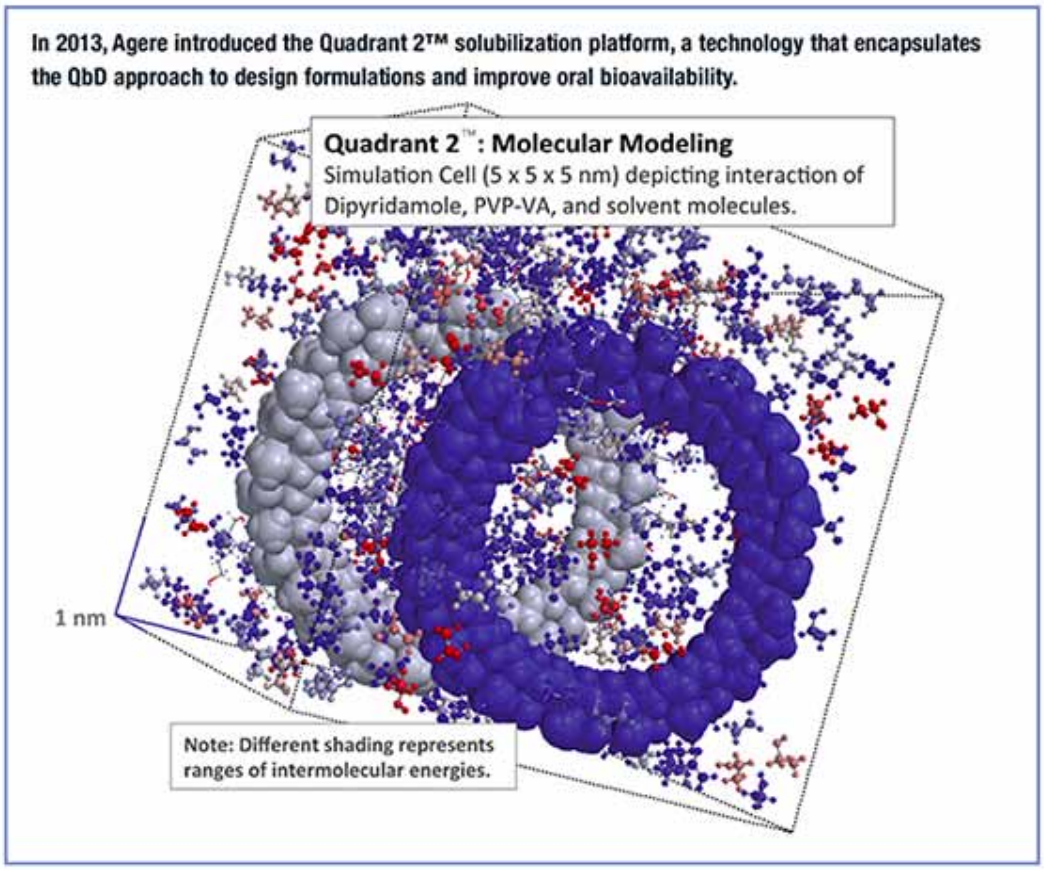
Agere is a CDMO specializing in solubilization formulation through amorphous solid dispersions to enhance oral bioavailability. The company offers solubilization formulation services through Phase II clinical trials materials manufacturing. Agere’s global client base ranges from virtual and small-size companies to mid-size and Top-20 pharmaceutical firms. All services are offered on a fee-for-service basis.

It’s no coincidence that Agere’s service offerings are based on trends the CDMO sees in the marketplace. According to Casey Jones, Vice President, Corporate Development, the company is experiencing an increase in demand for assistance in solubilization formulation, as the types of drugs in development that are poorly soluble is growing. “We performed an analysis that shows

that approximately 10% of all drugs that have been approved in the last decade had relied on solubilization technologies; we expect that this represents a sort of "tip of the iceberg" as a greater number of compounds in development face solubility issues."

QbD is being embraced broadly in the industry for scale-up and manufacturing, which delivers increasing advantages and lowers the cost of drug development. "We believe adopting a QbD approach even earlier, at the formulation design stage, will become essential," says Ms. Jones. "The benefits of bringing this discipline to formulation include greater efficiencies as iterations toward the client goal are minimized and overall risk to the project is reduced."

In 2013, Agere introduced the Quadrant 2(TM) solubilization platform, a technology that encapsulates QbD principles and is guided by the client's API and QTPP (Quality Target Product Profile) to design formulations that not only improve oral bioavailability, but also meet the overall goals for the drug product.



"For CDMOs, it's a balancing act to meet the client's requirements for a formulation that is optimal for their API and at the same time delivers an efficient path to the clinic," says Ms. Jones. "The Quadrant 2 QbD-based platform facilitates the process by providing a rigorous up-front "set-up" of the problem." This defines the ultimate solution space for the desired drug product. Two major benefits accrue. "By focusing on the targeted solution space, we eliminate the least-likely excipient candidates and invest program effort on optimization of the most probable to achieve stability, performance, and manufacturability requirements. And by relying on the agnostic analyses enabled through experimentation and modeling, the excipient candidates that emerge are not limited to ones that could have been predicted had we solely relied on experience."

And Agere continues to meet the needs of its clients. Through early integration of the formulation and process development, Agere operations utilize a detailed technical transfer plan, bringing on new equipment capabilities, as required, and ensuring plant availability to deliver when requested.

"As standards are adopted throughout the development process from formulation through commercial manufacturing, the ability of clients to choose the best-in-class at each stage becomes a reality," says Ms. Jones. "With a streamlined and standardized interface between each phase, our clients will be empowered by the best quality option for each part

of a program. Since the desire for a one-stop-shop approach remains strong, there will be increasing pressure on CDMOs to deliver competitive quality and value at every stage."

BEND RESEARCH/CAPSUGEL'S DFS—SCIENCE & ENGINEERING TO MEET TOUGH FORMULATION CHALLENGES

Capsugel is a global leader in delivering high-quality, innovative dosage forms, and solutions to its customers in the healthcare industry. The company sells nearly 60% of the world's hard capsules, with a broad portfolio of gelatin, vegetarian, and other specialized capsule technologies. Capsugel's Dosage Form Solutions (DFS) business unit was formed in 2013 with the addition of Bend Research (acquired in October 2013); Encap Drug Delivery (acquired in March 2013); and Capsugel's pre-existing research and manufacturing operations. Now combined under a single banner, Capsugel's DFS is a leader in drug delivery technologies and formulation development. Formulation offerings include technologies for oral bioavailability enhancement, modified release, taste-masking, and other specialized areas including pulmonary drug delivery, abuse deterrence, and biotherapeutic formulation and production.

"Capsugel's DFS business unit accelerates and improves product development through an array of proprietary technologies including lipids and liquids, spray-dried dispersions, hot-melt extrusions, and through specialized manufacturing, including FDA/MHRA-accredited finished dosage sites that can handle highly potent, controlled substance, hormonal and oncology compounds," describes Doug Lorenz, Vice President, Applied Technology at Bend Research. "In the area of bioavailability enhancement, our comprehensive technology offering includes amorphous dispersions (produced by spray-drying or hot melt extrusion), lipid formulations, micronizing and nanotechnologies, and formulations based on conventional and lipidic salt forms," says Mr. Lorenz. "Our clients include small biotech companies to large pharma. We support programs from early stage discovery through commercial manufacture."

A custom-spray dryer at Bend Research.

Capsugel's DFS provides clients with a science-based approach to select the optimum solution to bioavailability enhancement based on molecular properties and target product profiles, as well as customer preferences. Growth areas for Capsugel's DFS include development and manufacture of formulations for inhalation, and formulation and manufacturing support for biotherapeutic molecules.

Based on the company's formulation experience, Mr. Lorenz says a key trend in the pharmaceutical industry is the advancement of increasing numbers of compounds with low solubility. It is estimated that more than half of all new chemical entities have poor bioavailability because of low solubility. Capsugel's DFS offers technologies that enable the delivery of low-bioavailability compounds, including amorphous formulations prepared by spray drying and hot-melt extrusion, nanocrystalline formulations, and lipid-based/self-emulsifying formulations.

In the past year, Mr. Lorenz explains how Capsugel's DFS helped a small biotech client that was encountering low bioavailability for a compound in a preclinical development program and how Capsugel's DFS helped seek out a solution that could be implemented rapidly, using small quantities of API at a modest cost. "From the properties of the molecule, we were able to use our formulation models and bulk-sparing methods to identify a spray-dried amorphous formulation using less than 200 mg of API," he explains. "After achieving positive in vitro test results, we rapidly

manufactured 20 grams of spray-dried dispersion (SDD) for use in range-finding toxicology studies. This body of work was completed in less than 3 weeks from the initial evaluation to shipment of study supplies. Based on successful results and the high bioavailability obtained in these studies, the client requested larger-scale manufacture of SDD to support regulatory safety studies."

As this example illustrates, Capsugel's DFS establishes a long-term, alliance-based relationship as a development-team partner. "This close relationship with our clients enables optimal scientific interaction, provides for efficient communication, and facilitates rapid progression toward program goals. Our clients tell us that our broad, full-service capabilities make us the ideal development partner," says Mr. Lorenz.

GATEWAY ANALYTICAL—A NICHE IN INVESTIGATIONS & PARTICLE SIZING

Gateway Analytical is a multi-faceted analytical testing laboratory focusing on niche areas of pharmaceutical testing and investigations. Its client base spans the entire gamut of the pharmaceutical drug market from development to manufacturing. Its chemically specific particle sizing services have been focused on supporting the generic drug industry by providing detailed analysis to help developers establish bioavailability and prove bioequivalence, with Raman Chemical Imaging, which has proven to be a game changer when dealing with identifying the chemical makeup agglomerates, aggregates, and polymorphs, explains David Exline, Vice President of Gateway Analytical. Over the past year, Gateway Analytical has offered new services in the areas of glass delamination testing, automated particle identification with combined Raman/LIBS analysis to characterize overall populations of foreign particulate, and expanded services in the area of chemically specific particle sizing.

"Pharmaceutical investigations revolving around foreign particulate appears to be a major trend within the market," explains Mr. Exline. There are many challenges associated with the characterization of foreign particulate in the pharmaceutical industry. The main reason for this is the combination of materials that make up an end product. "Whether the goal is to identify a material, determine failures and product defects, perform reverse engineering investigations, identify foreign materials, or maintain quality of the product, the understanding of mixtures is critical in this analysis."

Within its chemically specific particle sizing group, Gateway has seen growth in the need to size and characterize agglomerations in drug products as this issue has significant impact on the drug quality and provides significantly more information about a product compared to conventional particle sizing methods.

One example would be the application of chemically specific particle sizing to a generic formulation compared to an innovator product. "A client can utilize this method to address the FDA critical path opportunity for generic nasal

suspensions formulations by providing the accurate and precise drug particle size measurement to demonstrate bioequivalence and save a considerable amount of time and money by being able to potentially wave the in vivo biostudies," he describes.

Mr. Exline believes that the trend for future formulation and manufacturing outsourcing will involve the need for detailed information of foreign particulate and API/excipient components on a particle-by-particle basis. "Historically, many bulk analytical methods have been satisfactory for characterization of materials," he says. "With the increasing scrutiny in the areas of foreign particulate investigations and the need to better understand API-excipient and API-API agglomerations, the need for highly specific single-particle characterization methods will become increasingly important."

MAINE BIOTECHNOLOGY SERVICES—SPECIALIZING IN ANTI-ID SCREENING

MBS provides monoclonal and polyclonal antibody services, from design and development to production, characterization, and assay development. MBS works with both pharmaceutical and diagnostic companies to develop antibodies against their targets of interest, which may include small molecules, recombinant antigens, peptides, and anti-idiotypes. Tools such as MultiPure technology and Octet Red kinetic analysis are used to allow customers the opportunity to refine their clone selection earlier in the process. The antibodies developed by MBS are used by customers to support therapeutic product release and clinical trials, as well as within their 510K-approved diagnostic kits.

As Carrie Rice, Sales Director at MBS, explains, "Our pharmaceutical customers increasingly have a need to develop anti-idiotypic antibodies for antibody neutralization assays. Anti-Id antibody candidates are screened for the ability to neutralize or block specific ligand binding of a therapeutic antibody. Monitoring therapeutic antibodies in clinical samples requires the ability to differentiate between administered antibody and naturally occurring endogenous antibodies. This has become increasingly difficult as antibody biotherapeutics more closely resemble circulating human immunoglobulins. Anti-idiotypic antibodies specific for the unique variable region of the therapeutic antibody are ideal for this purpose."

The most common end applications for anti-id antibodies developed at MBS are in the space of preclinical research for therapeutic antibodies. They can be used as reagents in pharmacokinetic studies, immune response immunogenicity assays, in ligand binding or neutralizing studies, or in antibody blocking assays.

In the past year, MBS has built on 25 years' experience in hybridoma development to offer anti-idiotypic antibody development. "For some of our pharmaceutical customers, developing the research use assays required for drug monitoring is a challenge or distraction that they do not want to divert their internal R&D resources to. In order to respond to that customer need, MBS has added assay development services to our offerings so that we may assist the customer one step further in the process," explains Ms. Rice. "We are now regularly evaluating antibody performance in sandwich ELISAs and bridging assays for customers. Pharma customers can now take clones with known performance and supporting data straight to their CRO for clinical assay development."

Ms. Rice describes one client's antibody development program. "One of our customers was faced with a challenge that we hear from so many: Get a companion assay up and running as soon as possible so that we can get our clinical trials going. As MBS had been part of the original antibody development program, we went back to our inventory and revived antibodies that had already been developed. We optimized assays that had already been used in the development program and made them robust and repeatable enough to be transferred to a clinical lab for assay development work. Had our customer gone back to square one, developing an assay could have added 9-12 months and tens of thousands of dollars to their program."

MBS finds itself in an evolving market and that could affect the service pharma customers can expect from providers. "The industry is experiencing a wave of acquisitions and outsourced manufacturing by antibody service providers to overseas providers. Sometimes that outsourcing is obvious and sometimes it is not made clear to the customer. Often, the pricing for projects undercuts the service providers that have longevity here in the United States. The risk, in our view, is that as the industry trends toward needing more and complex hybridoma developments in the anti-idiotypic space," she says. "Base model providers with canned approaches will likely not be able to meet the growing challenges that anti-idiotypic developments present."

METRICS INC.—TACKLING BIOAVAILABILITY

Metrics Inc. provides solid oral dose pharmaceutical development and manufacturing services to pharmaceutical industry clients worldwide. Areas of expertise include formulation development, first-time-in-man formulations, and

clinical trial materials manufacturing for Phase I, II, and III trials leading to commercial-scale manufacturing, and analytical method development and validation services. Formulation development services include handling insoluble and unstable actives, potent and toxic actives, and small molecule delivery. Instant-release and controlled-release tableting, capsule filling, overencapsulation, milling, micronizing, and enteric coating are also offered.

The CDMO is finding that the formulation development market has been faced with an increasing proportion of drug substances that are BCS II (Biopharmaceutics Classification System, category II) that need enhanced bioavailability techniques. These techniques run the gamut from IP-based spray drying and new excipients to requests to use common practice equipment, including milling, sieving, and the addition of polymeric materials, explains Jeff Basham, Vice President of Business Development at Metrics. Drug substance salt or polymorph manipulations also can be used to help this process.

Metrics Inc. has begun offering a novel drug delivery technology called SUBA® (Super Bioavailability) that involves co-processing of the poorly water-soluble API with a cellulosic enteric polymer. Co-processing is the means by which the particle size is reduced and further re-crystallization of the active ingredient is hindered by the presence of the enteric cellulosic polymer. The smaller particle size of the water-insoluble API allows for a higher level of bioavailability in the small intestine.

Scientists at Metrics, Inc. are working for enhancement of bioavailability techniques to respond to market demand.

“The benefit of SUBA is the development of an affiliated technology that uses an *in vitro* analytical technique to test whether we’ve successfully achieved a submicron particle size distribution of the poorly soluble API,” says Mr. Basham. “A Big Pharma sponsor wants to know right away whether SUBA technology is even applicable to the API, so the use of *in vitro* testing allows us to determine pretty quickly whether SUBA is applicable to that particular product.”

When applied successfully, SUBA can deliver therapeutic and convenience benefits that include reduced dosing frequency, increased patient compliance, improved side effect profile, and a more constant therapeutic effect.

Mr. Basham explains that SUBA was successfully used in the reformulation of itraconazole, an anti-fungal drug that has been available on the market in 100-mg dosage form. At that dosage form, itraconazole had been known to cause several side effects that are not beneficial to patient compliance. By employing SUBA technology, itraconazole has been reformulated such that patients are exposed to just half the amount of itraconazole per dosage form as before, he says.

“Anytime you can reduce the amount of API and still deliver the same amount of effective use of it, you mitigate the possibility of side effects. The U.S. Food and Drug Administration is always looking for a reduction in side effects or an increased level of safety and potential patient compliance.”

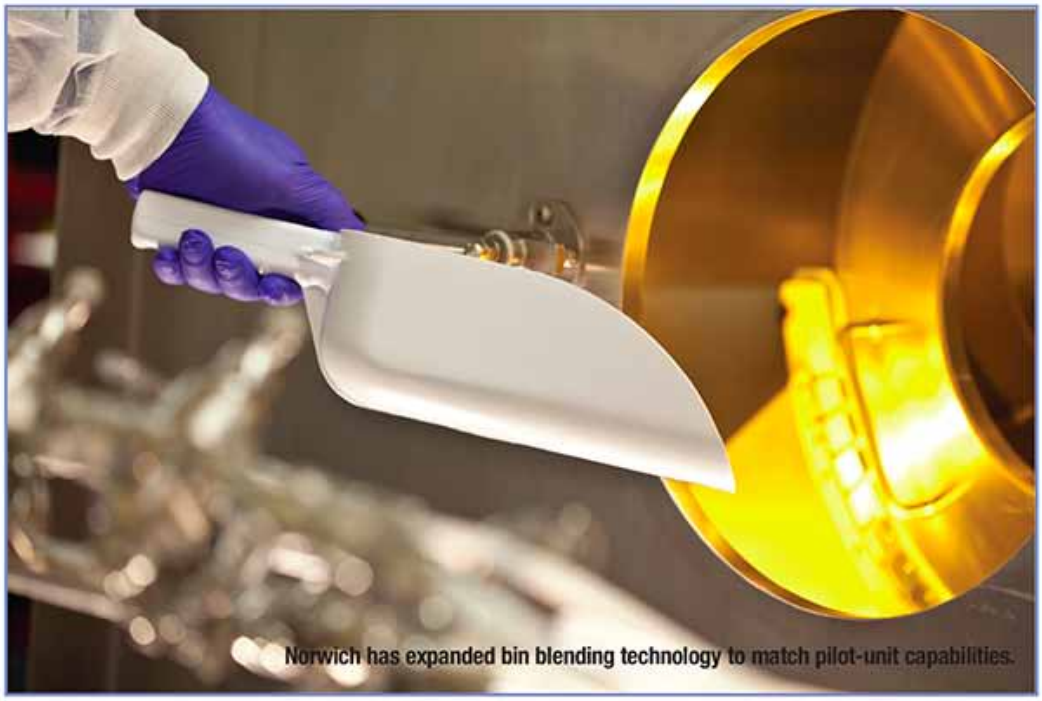
NORWICH PHARMA SERVICES—ONE SITE DOES IT ALL

The Norwich Pharma Services manufacturing facility located in Norwich, NY, offers contract development and manufacturing services with a focus on synchronized outsourced solutions from a single provider. Norwich offers services thatproducts, which makes bringing those products to market faster and more cost-effective, claims Stephanie Ferrell, Senior Manager, Marketing Communications at Norwich. “This single-destination facility offers customers, from large pharmaceutical companies to virtual organizations, a full range of services along the supply chain. From buying API to product distribution, Norwich has the capabilities for Phase I to III product development within the walls of the facility.”

While the company’s predominant focus is in developing and manufacturing solid oral dose, tablets, and capsules, Norwich also provides liquid dose services. Unit operations range from blending, encapsulation and coating to fluid bed, blister packing, and liquid fill packaging.

According to Ms. Ferrell, customers are looking for service providers that will be long-term partners. “The opportunity to work with a provider starting in early Phase I through commercial manufacturing gives customers a continuity of service while saving them time and money from having to move their project to other facilities for different phases. Thus, service providers need to be able to offer a wide breadth of services while having the flexibility and scalability to make sure that customer needs are met,” she says.

On the commercial manufacturing side, Norwich has expanded its blending technology options by adding bin blending to match pilot-unit capabilities. “Many newer products are being processed using bin blenders because they offer the potential for better uniformity and to overcome obstacles in product robustness,” explains Ms. Ferrell.



Norwich has expanded bin blending technology to match pilot-unit capabilities.

Norwich strives to offer flexibility with new technologies while maintaining legacy v-blending capabilities for customers not interested in moving their products to a new technology. Additionally, low humidity capabilities have been expanded to handle products down to a 30% humidity environment, and packaging capabilities have been expanded to provide an increase in packaging speed from 25%-50%, depending on bottle size.

Norwich’s depth of project management experience was highlighted when a customer presented a controlled-release tablet that required technical development and scale-up manufacturing, explains Ms. Ferrell. Key challenges for the drug formulation included temperature control, coating sensitivity, and clarity. In addition, the sensitive tablet coating process could impact the release profile of the drug through one or more laser-drilled holes. “Norwich immediately focused the project to design process parameters that control the quality of coating as well as its final clarity,” she says.

The Norwich team learned how to operate and perfect the innovative laser drill process technology used for the complicated potent compound. Equipment installation was performed in a room designed to meet stringent Class 1

Division 1 standards and minimize potential risks to personnel and environment.

“In collaboration with the customer, the Norwich team emerged as specialists on how to operate the new equipment but also optimized the design of the laser drilltechnology because of the focus of the project team. There were no regulatory issues to report and the tech transfer was on time, as defined in the project plan, despite the need to cross over from the pilot plant equipment to commercial operations. Norwich also successfully filed two registration batches –both completed 100% right the first time in support of an FDA filing.”

PARTICLE SCIENCES, INC.—A VARIETY OF FORMULATION APPROACHES

Particle Sciences, Inc. is an integrated provider of drug development services. Particle Sciences focuses on BCS II/III/IV molecules, biologics, and highly potent compounds through a variety of technologies, including emulsions, gels, micro- and nanoparticulates, drug/device combination products, and solid solutions. Through a full range of formulation, analytic, and manufacturing services, Particle Sciences provides pharmaceutical companies with a development solution that minimizes the time and risk between discovery and the clinic.

In the past year, Particle Sciences increased its offerings around GMP nanomilling, hot-melt extrusion, and spray drying to address formulation of BCS II molecules, explains Robert. W. Lee, PhD, Vice President, Pharmaceutical Development Services, Particle Sciences, Inc. In the second quarter of this year, the company will be offering a proprietary pro-drug approach that drastically increases the solubility of BCS II molecules. This will offer an alternative to nanoparticles for parenteral delivery of insoluble compounds, claims Dr. Lee.

Throughout the formulation process, Particle Sciences incorporates a Quality by Design (QBD) approach using modeling and Design of Experiments (DoE) to arrive at the best product with the strongest regulatory package. “One of our clients had a sterile emulsion that it wanted us to manufacture under GMPs using our M110EH Basic Biopharma Microfluidizer. At the requested scale of 120 L, the number of passes was prohibitive and by using a DoE approach, we were able to reduce the number of passes sufficiently to allow for an acceptable manufacturing process,” explains Dr. Lee.

As this example demonstrates, CDMOs are no longer simply a set of hands. “Clients expect a high level of basic science competency and sophisticated processing capabilities. A well-positioned CDMO needs to be able to lead a development effort.”

PATHEON—SOLVING SOLUBILITY & FLOWABILITY PROBLEMS

Patheon Inc. is the pharmaceutical services business owned by DPx Holdings. The company is a leading provider of CDMO services, pharmaceutical products, and products for other industries. With global headquarters in Durham, NC, DPx has a footprint of 24 locations across North America, Europe, Latin America, and Australia. Patheon provides preclinical, clinical formulation development (Phase I to III), scale up, and process development of solid oral and sterile dosage forms. In addition, Patheon provides registration batch manufacturing, process validation, QbD, and small- and large-scale commercial manufacturing.

“We undertake formulation and process development of a variety of dosage forms – simple solid oral forms in early-stage clinical development and late-stage clinical development such as powders, granulates, capsules, tablets, softgels, sterile liquids, lyophilized powder in vials, and prefilled syringes,” describes Anil Kane, PhD, Executive Director, Global Formulation Sciences, PDS, Patheon.

The dosage forms developed are immediate release as well as controlled release forms in a variety of technologies to meet the dosage profile for clinical therapeutic efficacy. Patheon also offers formulation development and manufacturing services in life cycle management for pediatric dosage forms, fixed-dose combinations as multi-layer tablets, multiparticulates, beads, minitablets, etc.

Because of its support of clinical and commercial development and manufacturing services, Patheon has a keen sense of formulation trends. For instance, Dr. Kane says that an increasing number of new chemical entities being created out of drug discovery in the preclinical stage exhibit poor aqueous solubility and poor bioavailability. “These compounds pose significant challenges in solubilization, absorption, and permeation on oral administration. The efficient formulation of these compounds requires expertise in the techniques and technologies that can deliver the drugs into the systemic circulation by improvement in bioavailability."

He also points out a rising number of products being developed as line extensions or as part of a life cycle management strategy. “Development of modified release, controlled-release dosage forms, and active drug layering are on the rise,” he says.

And, due to the regulatory changes in Europe and North America, Patheon also sees an increase in demand for pediatric formulation development of many new clinical drug candidates. “A significant number of fixed-dose combinations of two or more new chemical entities, or a combination of NCIs plus an off-patent for existing drugs are being developed and tested in clinical trials for existing or newer indications,” Dr. Anil explains. “Based on the drug dosage profile required, its site of absorption, maximum therapeutic efficacy, and its stability with other active ingredients, a multi-layer tablet, bi or trilayer, a tablet in a tablet, multi-particulates in a capsule are being developed to address the need of the clinical studies and for marketing approval.”

In the past year, Patheon launched the “Early Development” service in Cincinnati and at its Milton Park site near Oxford, UK, to address API characterization, formulation screening, clinical formulation manufacture, and stability studies. The company also launched development and commercial manufacturing services of softgels as standard softgels, and using its patented technologies to target the drug at various regions of the gastro-intestinal tract. Patheon has invested in Phase II scale manufacturing capabilities at the Milton Park site. In addition, Patheon is also investing in equipment and capability of handling high potent compounds at these early development centers.

Through formulation development, Patheon has solved low-solubility problems and developed formulations with significantly higher exposure in animal model or first-in-man clinical studies. The increase in bioavailability was achieved using one or the other techniques from the tool kit – micronization, micro fluidization, lipid-based solubilization, or by solid dispersion techniques such as spray drying or hot-melt extrusion.

Patheon has also addressed problems of poor flowability of active drug substance powders, and developed manufacturing and scalable processes that can support commercial large-scale manufacturing. In the area of sterile dosage forms, several projects have been successfully completed where a formulation was developed to stabilize the drug in a sterile solution and monitor the physical and chemical stability over a period of time.

PHARMATEK—MEETING FORMULATION CHALLENGES

Pharmaek is a full-service dosage form development and GMP manufacturing services organization. Services include preformulation testing, analytical and formulation development, GMP manufacturing, clinical packaging, labeling and distribution, and stability testing and storage. With 15 years of experience developing small molecules and peptides for oral and injectable delivery, Pharmatek specializes in the development and manufacture of challenging compounds and complex formulations, including poorly soluble NCEs and controlled-release formulations.

According to Elizabeth Hickman, Associate Director, Marketing, Pharmatek, the need for formulation and

manufacturing technologies that address poor solubility continues to increase.

At the same time, companies want the most efficient and cost-effective route to the clinic to establish compound efficacy. “Technologies such as API-in-Capsule and simple blend formulations in Phase I are an attractive solution for companies that want to reduce investments in the early stages,” Ms. Hickman says. “Previously, we had only seen this strategy used by virtual and small pharmas, but now see this strategy being utilized more and more by our large pharma clients.”

When a phase-appropriate strategy makes sense for the compound and the client’s objectives, Pharmatek’s objective is to select the least complex formulation approach that provides acceptable in-vivo performance. “In some cases, this cannot be achieved without the use of more complex formulation technologies,” says Ms. Hickman. “In those cases we will utilize our broad experience with the development of amorphous dispersion, lipid delivery, fluid bed processing or melt granulation.”

In Pharmatek's new packaging line, an operator is filling the hopper with capsules before entering the bottle filler.

To determine the best route forward, Pharmatek will screen the compound against several formulation strategies in parallel, while using a minimum quantity of API. As Ms. Hickman explains, because the data is only as good as the method used to generate it, Pharmatek first starts with a solid stability-indicating analytical method, develops a thorough understanding of the compound's physiochemical properties, and develops a discriminating dissolution method for the evaluation of prototypes. Lead prototypes are then tested in-vivo before selecting a clinical formulation. "From bioavailability enhancement technologies for insoluble compounds to API-in-a-capsule, we match the best solution with the physiochemical characteristics of the compound and the company's corporate goals, clinical timelines, and development budget."

Pharmatek recently purchased an automated bottling and labeling line. The addition of the line is part of the company's ongoing investment to support increasing demand for larger scale productions. "Automatic bottling improves the

efficiency and accuracy of clinical packaging, resulting in a reduction in overall costs and time-to-clinic. Additionally, the new bottling line significantly increases Pharmatek's overall capacity, allowing higher throughput and larger GMP manufacturing runs," says Ms. Hickman.

To complement its toolkit of solutions for poorly soluble compounds, Pharmatek recently invested in particle size reduction technology with the addition of a Jet-OMizer Jetmill for the micronization of API. The company also recently added a Niro Mobile Minor Spray Dryer. The new spray dryer will complement current spray drying capabilities and enable the production of larger batches for early-phase clinical trials.

Pharmatek has seen a growth in the number of peptide compounds being developed in recent years. In the past year, the company has worked on seven peptides for early-phase development. Formulation strategies include suspensions, liquids, frozen liquids and lyophilized products. Each formulation strategy requires a thorough understanding of peptide chemistry and injectable development.

Because peptides are easily susceptible to degradation, well-developed orthogonal analytical methods are essential to successful formulation development. "We've dealt with diverse peptides and successfully implemented analytical methods to characterize the product and develop formulations designed to mitigate the risk of degradation."

XCELIENCE—OVERCOMING QBD CHALLENGES

Xcelience is a full-service CDMO that can manage the progression of a pre-IND API through the development process. A client's API can be fully characterized (salt and polymorph screens, intrinsic solubility, etc.) before formulation development. Xcelience can develop a range of formulations, including capsules, tablets, oral solutions/suspensions, and topical products, using technologies such as roller compaction, extrusion/spheronization, wet granulation, and self-emulsifying systems for liquid products. The formulations are then moved into GMP manufacturing.

According to Paul Skultety, PhD, Vice President, Pharmaceutical Development Services & Project Management at Xcelience, one of the biggest trends in formulation development is the incorporation of QbD principles in the development process. Formulation development must be performed such that critical quality attributes can be identified. This, in turn, will allow for critical process parameters to be evaluated and a risk assessment performed using tools such as Failure Modes and Effect Analysis to help determine which parameters might impact the process. The parameters that have an impact on the critical quality attributes can be evaluated using appropriate statistical study designs. "The data from these studies can be used to develop the design space (ranges for these parameters) for each critical process parameter," describes Dr. Skultety. "By identifying and controlling these parameters, the product will have the desired quality characteristics. The design spaces will assist in determining in-process testing limits and the finished product specifications." The data can further be applied to help justify the validation plan that will be used once the product moves to commercial scale.

In addition to QbD, another trend that Xcelience has identified is the need to develop pediatric dosage formulations sooner in the life cycle of a new compound. "In a number of cases, we have been asked to develop a pediatric formulation with an acceptable flavor (taste) before filing the adult dosage formulation," says Dr. Skultety. "We have developed several pediatric formulations including chewable tablets, sachets, and oral liquids. Because these were new molecules, the taste properties of the formulations were evaluated using a model compound. This allowed for refinement of the formulation and the development of an acceptable-tasting final formulation."

While reformulating taste can be a challenge, Xcelience was also faced with the challenge of an extremely adhesive compound. “It was a fairly high-dose compound, which further exacerbated the problem,” he explains. “No matter how much lubricant was used, the compound would always stick to the punches. Our scientists were able to develop a processing technique that allowed for the tablets to be compressed on the high-speed tablet press with no build up on the punches.”

Going forward, Dr. Skultety expects that more companies will be outsourcing their formulation development. “It is difficult for small and mid-size companies to have the needed breadth of expertise and equipment in-house to handle all that is involved in this area. It is a tremendous expense to build a GMP facility, purchase the needed equipment to handle the various batch sizes, and then maintain the facility,” he says. “If a company does have a larger portfolio of compounds, it is more cost effective and faster for it to outsource the formulation development, the analytical work, and stability studies.”

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